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PRINCIPAL INVESTIGATOR: Nathaniel M. Fried, Ph.D.

CONTRACTING ORGANIZATION: Johns Hopkins University School of Medicine
Baltimore, Maryland 21205-2196

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Nathaniel M. Fried, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Johns Hopkins University School of Medicine
Baltimore, Maryland 21205-2196

E-Mail: nfried@jhmi.edu

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Urethral and bladder neck strictures occur in 5-20 % of all prostate cancer surgeries, resulting in urinary incontinence. Conventional treatments for stricture have widely variable success rates with sub-optimal longterm results. The failure of these treatments is presumably due to mechanical and/or thermal damage to the urethral wall during the procedure. The purpose of this research project is to test a new laser, the Erbium:YAG laser, which is capable of precisely incising the urethral stricture with minimal peripheral damage to adjacent healthy tissue. We hypothesize that minimal side-effects caused during Erbium laser incision should translate into limited scarring and improved procedural success rates. Year #1 of this project was devoted to optimization of the laser and optical fiber delivery system for rapid and precise cutting of urethral tissue. We accomplished these tasks, and published our findings in the form of four manuscripts and two abstracts. Year #2 of this project was devoted to *in vivo* animal studies comparing the wound healing after Erbium and Holmium laser incision of the urethra and bladder neck. Further improvement of the optical fiber delivery system was also accomplished. We have published our findings in the form of five manuscripts and two abstracts.

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TABLE OF CONTENTS

INTRODUCTION

Urethral and bladder neck strictures occur in 5-20 % of all prostate cancer surgeries, resulting in urinary incontinence. Conventional treatments for stricture (including balloon dilation, cold knife incision, electrocautery, and Holmium laser incision) have widely variable success rates with sub-optimal long-term results. The failure of these conventional stricture treatments is presumably due to mechanical and/or thermal damage to the urethral wall during the procedure. The purpose of this research project is to test a new laser, the Erbium:YAG laser, which is capable of precisely incising the urethral stricture with minimal peripheral damage to adjacent healthy tissue. We hypothesize that the minimal side-effects caused during Erbium laser incision should translate into limited scarring and improved procedural success rates. Year #1 of this project was devoted to optimization of the laser and optical fiber delivery system for rapid and precise cutting of urethral tissue. We accomplished these tasks, and published our findings in the form of four manuscripts and two abstracts. Year #2 of this project was devoted to *in vivo* animal studies comparing the wound healing after Erbium:YAG laser and Holmium:YAG laser incision of the urethra and bladder neck. Further improvement of the optical fiber delivery system was also accomplished as a continuation of previous work. We have completed these tasks, and published our findings in the form of five manuscripts and two abstracts. One of the tasks in Year #2 was not completed because the grant reviewers stated that the task was flawed and should not be addressed.

BODY

Statement of Work (Year #2)

Task #3: Study wound healing process after Er:YAG laser incision of normal urethra (Months 13-18).

a. Perform acute studies for comparison with ex vivo results from Task #1 to determine effect of hydration and perfusion on ablation parameters.

Status – COMPLETED
Acute, *in vivo*, Er:YAG laser incisions produced 20 ± 5 µm of thermal damage, comparable to the 10-20 µm measured during previous *ex vivo* results, and much smaller than the 660 ± 110 µm, measured for the conventional Holmium:YAG laser.

b. Conduct short-term chronic wound healing study to confirm minimum urethral scarring after Er:YAG laser incision.

Status - COMPLETED
Short-term chronic wound healing studies were conducted in a pig animal model with healing for up to 14 days. Erbium:YAG laser incisions produced 430 ± 100 µm of thermal damage, 4 times less thermal damage than the conventional Holmium:YAG laser, which produced a thermal damage zone of 1580 ± 250 µm.

Task #4: Develop improved animal model for creating strictures (Months 19-26).

a. Create strictures in a porcine model using both electrocautery and Nd:YAG laser instruments.
Status – NOT COMPLETED*

b. Quantify degree of thermal damage and lumenal narrowing and which instrument provides most consistent stricture creation.
Status – NOT COMPLETED*

* Note that Task #4 was not completed in this project. During the review of this grant proposal, the reviewers stated that Task #4 was flawed and should not be addressed - "Specific Aim 4, which deals with the animal model, has serious weaknesses and should be eliminated. The panel recommends that the investigators concentrate on the other four specific aims."

In agreement with the reviewers' comments, we have concentrated on successfully completing the animal studies described in Task #3 and further improving upon previous results of the development of an optical fiber delivery system from Task #2c. We have now completed 3 out of 4 of the tasks. In Year 3, we will focus on completing Task #5, the final task of this research project.

Below is a summary of work performed to complete Task #3 and to improve upon results from Task # 2c.

TASK #3a: Perform acute studies for comparison with ex vivo results from Task #1 to determine effect of hydration and perfusion on ablation parameters.

Problem: Previous ex vivo tissue studies demonstrated that the Erbium laser was capable of precise incision of urethral tissue with a thermal damage zone of only 10-20 µm. This thermal damage zone was much less than that of the Holmium laser which produced 300 µm of thermal damage. However, it is necessary to perform more realistic in vivo animal studies to determine whether differences in tissue hydration and perfusion will effect our results.

Solution: We performed in vivo animal studies in a pig animal model using both the Erbium and Holmium lasers. H&E stained histologic cross-sections of the tissue were examined using optical microscopy and the thermal damage zone measured quantitatively. Collateral thermal damage at Day 0 measured 20 ± 5 µm for the Erbium laser and 660 ± 110 µm for the Holmium laser, thus verifying that the Erbium laser results are comparable to previous ex vivo results, and also much better than the conventional Holmium laser.

TASK #3b: Conduct short-term chronic wound healing study to confirm minimum urethral scarring after Er:YAG laser incision.

Problem: Although the Erbium laser produced minimal thermal damage during incision of the urethra and bladder neck, it is unclear how this thermal damage will translate into scar formation during the wound healing process.

Solution: Short-term, chronic wound healing studies were performed in pigs out to 14 days, to quantify scar formation after Holmium and Erbium laser incision. We demonstrated that there is 4 times less scarring after Erbium:YAG laser incision of healthy urethra and bladder neck as compared with the Holmium:YAG laser, after 14 days of wound healing. The Erbium:YAG laser incisions also healed twice as rapidly as Holmium:YAG laser incisions. For any given day of wound healing, there was also less granulation tissue and smaller incision depth for Erbium:YAG laser than Holmium:YAG laser.

METHODS:

Laser Parameters
An Er:YAG laser (SEO 1-2-3, Schwartz Electro-optics, Orlando, FL) operating at a wavelength of 2.94 µm, a pulse duration of 70 µs, fiber output pulse energy of 20 mJ, and repetition rate of 10 Hz was used. The laser radiation was focused into a 250-µm-core sapphire optical fiber (Photran, Amherst, NH). A Ho:YAG laser (SEO 1-2-3) operating at a wavelength of 2.12 µm, pulse duration of 300 µs, fiber output energy of 500 mJ, and repetition rate of 3 Hz, was also used. The laser radiation was focused into a 300-µm-core silica optical fiber (Table 1).

Table 1. Summary of laser parameters used in this study.

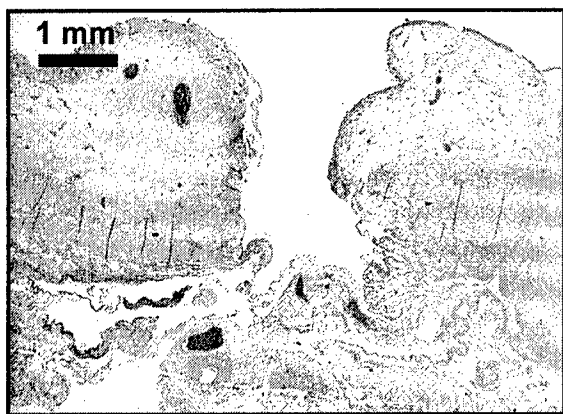| Laser Parameters	Holmium	Erbium
Wavelength (µm):	2.12	2.94
Energy / pulse (mJ):	500	20
Pulse Length (µs):	300	70
Pulse Repetition Rate (Hz):	3	10
Fiber Core Diameter (µm):	300	250
Fiber Type:	silica	sapphire

Animal Studies

All procedures were approved by the JHU Animal Review Committee (ACR# SW01M293). A total of 18 female pigs (30-45 kg) were divided into two arms, with 9 pigs in each laser arm. Three animals in each arm were sacrificed on postoperative days 0, 6, and 14. During the procedure, access to the urethra and bladder neck was obtained using a 17F rigid cystoscope with 30-degree lens. Three 1-cm-long incisions were made in each pig, two at the bladder neck and one in the mid-urethra. After the procedure a 14F urethral catheter was left in the bladder then removed after 3-4 hours. The pigs were euthanized, and the bladder and urethra samples were removed for histopathological processing. Quantitative measurements of collateral injury and incision depth were made. Collateral damage on day 0 was recorded as coagulative necrosis from the incision outward, while on days 6 and 14 as the extent of granulation width at the wound base. These parameters were analyzed using a Student's t-test.
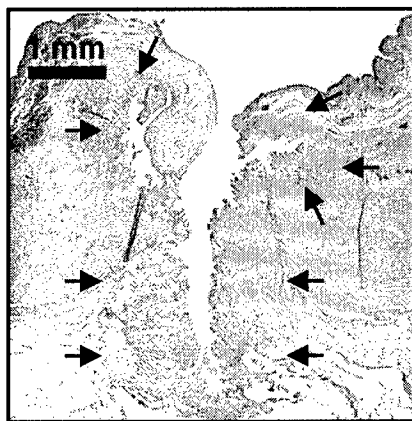
RESULTS

On day 0, Er:YAG and Ho:YAG laser incisions in the mid-urethra and bladder neck were of comparable depth, averaging 2540 ± 390 μm and 2530 ± 780 μm, respectively ($p = 0.49$) (Table 2). The zone of coagulative necrosis (Figure 1a-b) was significantly higher for the Ho:YAG laser than for the Er:YAG laser (660 ± 110 μm vs 20 ± 5 μm, respectively, $p = 0.01$). On day 6 (Figure 1c-d), the granulation tissue width at the incision base was 900 ± 100 μm and 2280 ± 700 μm, for the Er:YAG and Ho:YAG lasers, respectively ($p = 0.04$). After 14 days the granulation tissue created by the Er:YAG laser was less than the Ho:YAG laser (430 ± 100 μm vs 1580 ± 250 μm, respectively, $p = 0.03$) (Figure 1e-f). As wound healing progressed, granulation tissue filled the wound bed and decreased the incision depth. At day 6, the Er:YAG and Ho:YAG laser incisions were 45% and 60% of initial depth (1100 ± 200 μm vs 1500 ± 300 μm, respectively, $p = 0.04$). On day 14, the Er:YAG and Ho:YAG incisions were 25% and 50% of initial depth (670 ± 140 μm vs 1240 ± 140 μm), respectively ($p = 0.02$). Images of the tissue surface at 14 days also demonstrate accelerated wound healing after Er:YAG incision compared with Ho:YAG incision (Figure 2a-b).

Table 2. Injury parameters after incisions made with Ho:YAG and Er:YAG lasers at day 0, 6, and 14.
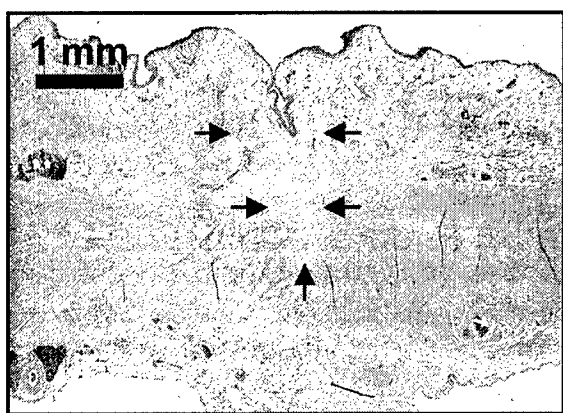
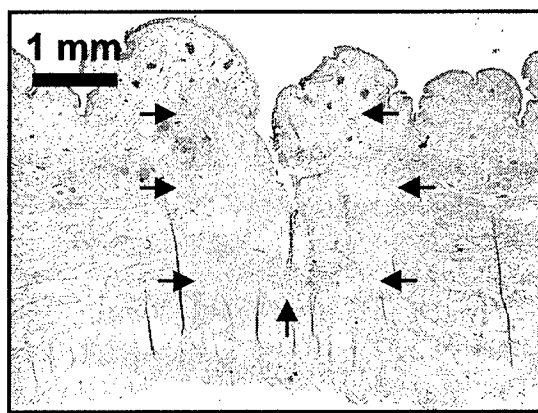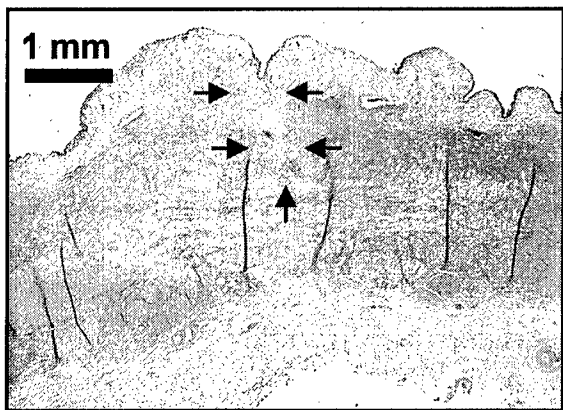| Laser	n	Day 0		n	Day 6		n	Day 14	
		Incision Depth (μm)	Thermal Damage (μm)		Incision Depth (μm)	Granulation Width (μm)		Incision Depth (μm)	Granulation Width (μm)
Holmium	3	2530 ± 780	660 ± 110	3	1500 ± 300	2280 ± 700	3	1240 ± 140	1580 ± 250
Erbium	3	2540 ± 390	20 ± 5	3	1100 ± 200	900 ± 100	3	670 ± 140	430 ± 100
P value		0.49	0.01		0.04	0.04		0.02	0.03

(a) Er:YAG, Day 0   (b) Ho:YAG, Day 0
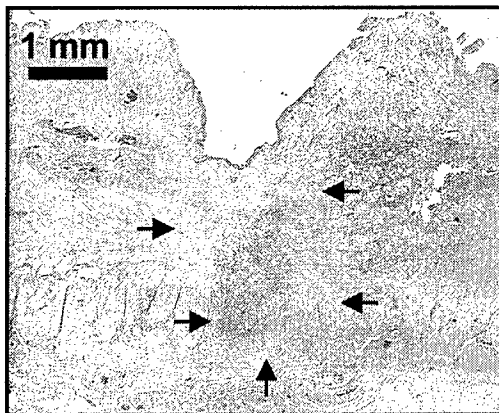
(c) Er:YAG, Day 6   (d) Ho:YAG, Day 6

(e) Er:YAG, Day 14   (f) Ho:YAG, Day 14

Figure 1. H&E stained histologic cross-sections of incisions made with the Er:YAG and Ho:YAG laser on post-operative days 0, 6, and 14. Arrows demarcate the border between native tissue and thermally coagulated tissue.

(a) Er:YAG, Day 14   **(b)** Ho:YAG, Day 14

Figure 2. Images of incisions made with Er:YAG and Ho:YAG lasers at day 14. (a) Er:YAG; (b) Ho:YAG.

This study confirms the minimal collateral thermal damage caused acutely by the Er:YAG laser by gross and histologic examination. Histologic examination demonstrated that the Er:YAG laser produced approximately four times less scar tissue than the Ho:YAG laser. The granulation zone and incision depth were also less in the Er:YAG laser arm than in the Ho:YAG laser for a given POD. Incisions made with the Er:YAG laser healed twice as rapidly as those with the Ho:YAG laser. This difference was also observed with tissue examination prior to formalin fixation. Er:YAG laser incisions at day 14 were difficult to identify because of almost complete healing.

TASK #2c (Revisited): Build hybrid fibers combining flexible germanium oxide trunk fiber with durable fiber tip to prevent fiber damage.

Problem: We previously designed hybrid germanium / silica fibers for use in endoscopic surgery. However, while these initial results proved promising for our research project, it was necessary to further develop and optimize these fibers before routine use.

Solution: We explored several different heat-shrink materials for attaching the fiber tip to the germanium trunk fiber, optimized the power transmission through these fibers, and also measured transmission rates and attenuation losses through the fibers. The results demonstrated that there is sufficient transmission of Erbium laser energy for use in endoscopic applications including laser incision of the urethra and bladder neck.

METHODS
A Schwartz Electro-Optics SEO 1-2-3 laser, operated with either an Er:YSGG (λ = 2.79 μm) or an Er:YAG (λ = 2.94 μm) laser rod, was used for the experiments. The laser was operated in free-running mode with a 300 μs pulse length and in short-pulse mode with a 500 ns pulse length produced by a rotating mirror Q-switch. The Q-switched Er:YAG and Er:YSGG laser pulse energy measured 25 mJ at 3 Hz. The laser pulse energy was measured using a Molectron EPM 1000 pyroelectric detector and the temporal pulse length was measured using a Boston Electronics PD-10.6 photovoltaic infrared detector. The laser radiation was focused with a 20-mm-focal-length calcium fluoride lens into hybrid germanium / silica optical fibers consisting of a 1-meter-length germanium oxide trunk fiber (Infrared Fiber Systems, Silver Spring, MD) with a 1-cm-length low-OH silica fiber tip. The trunk/tip fiber-core diameters measured 250/365, 350/365, and 450/550 μm and were attached with three different types of heat-shrink tubing: (a) PTFE, (b) PET, and (c) PTFE /

FEP combination (Table 3, Figure 3). A linear fit to the data points provided the average percent transmission of the fibers, which was then corrected by subtracting the Fresnel losses, and the attenuation calculated in dB/m. The data points for each graph represent the average of 7 independent measurements from 7 different fibers, and the error bars represent the minimum and maximum values recorded.

Table 3. Heat-shrink tubing materials used to connect hybrid fibers.

Material	Pre-/Post-Shrink ID (µm)	Wall Thickness (µm)	Shrink Temp. (°C)
PTFE	850 / 375	150	343
PTFE / FEP	900 / 0	575	343 / 17
PET	350 / 280	12.5	85-190
	450 / 360	12.5	
	725 / 580	25	

(a)

(b)

(c)

Figure 3. Hybrid germanium/silica fibers assembled using: (a) PTFE; (b) PTFE / FEP; (c) PET. A 1-cm-long, silica tip was attached to a 1-m-long germanium fiber. Germanium fiber diameters are 450, 350, and 250 µm. Ruler bar = 1 mm increments.

RESULTS

Hybrid Fiber Assembly
PTFE was found to be the most reliable material producing the highest Er:YAG pulse energy transmission, although the high shrink temperature resulted in melting of the Hytrel coating on the germanium fiber (Figure 1a). The PTFE / FEP shrink-melt combination produced the worst results. The shrink pressure and melted FEP tended to push the silica tip away from the germanium trunk fiber, causing sub-optimal alignment at the fiber interface and resulting in poor laser transmission

and low damage thresholds (Figure 1b). The major limitation of the PET tubing was its wall thickness (12.5 – 25 μm), which results in weak bending strength (Figure 1c). PET is also limited to only approximately 20% shrinkage, so the trunk and tip fiber outer diameters need to match more precisely than with PTFE. However, PET has some advantages: its low shrink temperature eliminates melting of the germanium Hytrel jacket, its transparency provides better alignment of the fiber interface, and it shrinks more uniformly than PTFE.

Peak Output Energies

Maximum hybrid fiber transmission of free-running Erbium:YAG laser radiation was measured (Table 4). The peak hybrid fiber transmission of Erbium:YAG laser energy was approximately 100 J/cm^2 for all of the fiber diameters (250/365, 350/365, 450/550) tested, with pulse energies reaching as high as 233 mJ at 10 Hz. Average fiber transmission measured approximately 70 J/cm^2 for these fiber diameters. Transmission of Q-switched Er:YAG laser energy was also measured through 450/550 hybrid fibers, with peak pulse energies of 13 mJ.

Table 4. Peak and average Er:YAG pulse energies transmitted through hybrid germanium / silica fibers.

| Fiber Core (μm) | Maximum | | Average | |
(Trunk / Tip)	Energy (mJ)	Fluence (J/cm^2)	Energy (mJ)	Fluence (J/cm^2)
250 / 365	103	98	74 ± 29	71
350 / 365	112	107	79 ± 24	75
450 / 550	233	98	157 ± 46	66

Transmission and Attenuation Measurements

The percent transmission of free-running and Q-switched Erbium:YAG and Erbium:YSGG laser radiation through 1-meter-length germanium oxide trunk fibers with a 1-cm-length low-OH silica tip was measured (Figure 4). Transmission rates for the free-running Er:YAG and Er:YSGG lasers measured 56% and 65%, respectively (n = 7 fibers). After correction for the Fresnel reflection losses at the fiber interfaces, the fiber attenuation measured 1.1 ± 0.1 dB/m and 0.6 ± 0.1 dB/m, respectively. The transmission rate for the Q-switched Er:YAG and Er:YSGG lasers was 55% and 65%, with an attenuation of 1.1 ± 0.2 dB/m and 0.9 ± 0.3 dB/m, respectively. Both Q-switched lasers transmitted a maximum pulse energy of 13 mJ (n = 7 fibers).

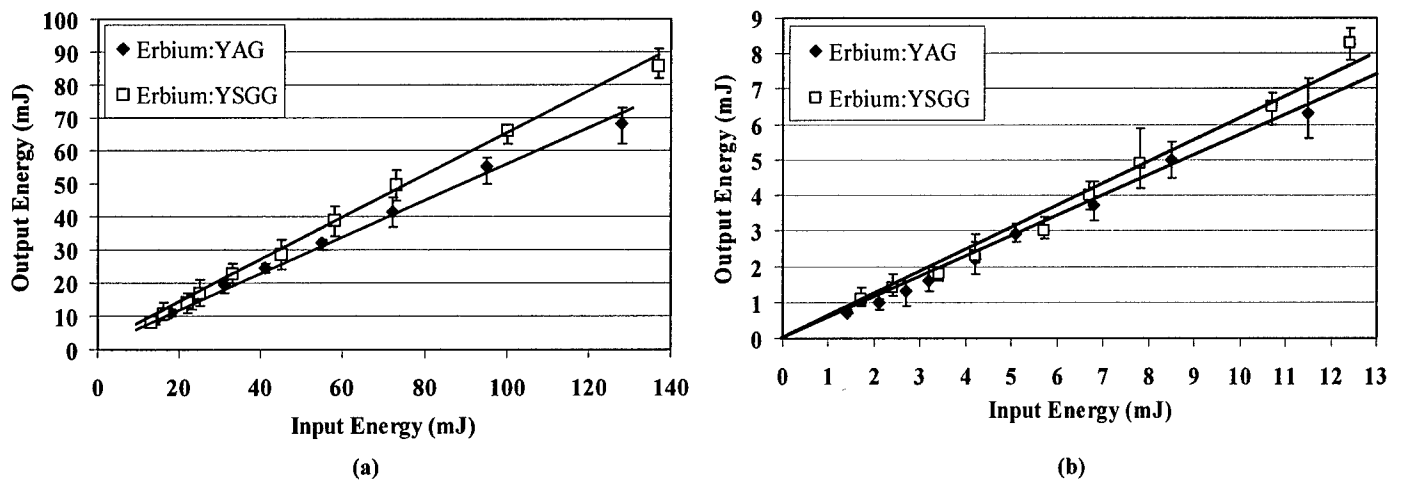
(a)

(b)

Figure 4. Hybrid fiber transmission rates for Er:YAG and Er:YSGG laser radiation during (a) free-running (300 μs) and (b) Q-switched (500 ns) operation. All fibers tested were 450 / 550 μm hybrid fibers.

In this study, we demonstrated a simple, biocompatible, and inexpensive method of assembling hybrid germanium / silica optical fibers using PTFE heat-shrink tubing. Peak hybrid fiber energies of up to 233 mJ at 10 Hz were transmitted through the fibers with the fluence reaching approximately 100 J/cm^2 for all the fiber diameters (250/365, 350/365, 450/550) tested. Although average pulse energies were lower and bending losses have previously been recorded, transmitted energies are still well above what is necessary for Er:YAG laser ablation of most soft tissues, which typically only require a fluence of 1-5 J/cm^2.

Tables 5 and 6 provide a comparison of free-running and Q-switched Er:YAG and Er:YSGG laser fiber transmission and attenuation between the hybrid fibers and previous studies characterizing the bare germanium and sapphire fibers. The attenuation through the hybrid fiber is significantly higher than that through the germanium and sapphire fibers. This is most likely due to coupling losses at the germanium / silica interface as well as the high attenuation through the silica tip. However, considering the relatively low pulse energies necessary to ablate tissue (a few mJ), the availability of high-power Erbium lasers (Joules/pulse), and the need for only a few meters of fiber length for most medical applications, a fiber attenuation of 0.6 – 1.1 dB/m is more than adequate.

Table 5. Percent transmission of Er:YAG and Er:YSGG laser radiation through mid-IR fibers.

Fiber Type/Size	Er:YSGG (λ = 2.79 μm)		Er:YAG (λ = 2.94 μm)	
	Free-running	Q-switched	Free-running	Q-switched
Sapphire (425)	88 $\pm$ 6	65 $\pm$ 3	77 $\pm$ 5	74 $\pm$ 4
Germanium (450)	76 $\pm$ 2	57 $\pm$ 1	68 $\pm$ 2	64 $\pm$ 6
Hybrid (450/550)	65 $\pm$ 2	62 $\pm$ 5	56 $\pm$ 3	55 $\pm$ 4

Table 6. Attenuation (dB/m) of Er:YAG and Er:YSGG laser radiation through mid-IR fibers.

Fiber Type/Size	Er:YSGG (λ = 2.79 μm)		Er:YAG (λ = 2.94 μm)	
	Free-running	Q-switched	Free-running	Q-switched
Sapphire (425)	0.2 $\pm$ 0.1	1.0 $\pm$ 0.2	0.4 $\pm$ 0.2	0.6 $\pm$ 0.2
Germanium (450)	0.3 $\pm$ 0.1	1.3 $\pm$ 0.1	0.7 $\pm$ 0.1	0.9 $\pm$ 0.3
Hybrid (450/550)	0.6 $\pm$ 0.1	0.9 $\pm$ 0.3	1.1 $\pm$ 0.1	1.1 $\pm$ 0.2

A novel, hybrid germanium oxide / silica optical fiber was optimized for the delivery of free-running and Q-switched Erbium:YAG and Erbium:YSGG laser radiation. Peak fiber transmission and attenuation was measured. Sufficient Erbium laser energy was transmitted for use in soft tissue ablation. This optical fiber is useful in endoscopic medical applications requiring a flexible fiber for contact tissue ablation, such as incision of urethral and bladder neck strictures.

KEY RESEARCH ACCOMPLISHMENTS

- Acute, *in vivo*, thermal damage zones measured 20 ± 5 μm for the Erbium:YAG laser (comparable to previous *ex vivo* results of 10-20 μm), much smaller than 660 ± 110 μm for Holmium:YAG laser. This result confirms our previous, *ex vivo*, studies reporting that the Erbium:YAG laser is 20-30 times more precise than the Holmium:YAG laser for incision of the urethra and bladder neck (Task 3a).

- We demonstrated that there is 4 times less scarring after Erbium:YAG laser incision of healthy urethra and bladder neck as compared with the Holmium:YAG laser, after 14 days of wound healing in a pig model. The Erbium:YAG laser incisions also healed twice as rapidly as Holmium:YAG laser incisions. For any given day of wound healing, there was less granulation tissue and smaller incision depth for Erbium:YAG laser than Holmium:YAG laser (Task 3b).

- We characterized the hybrid fiber transmission rate, attenuation rate, and maximum pulse energy that the fiber can deliver for endoscopic applications in urology. The hybrid fiber was improved to deliver a maximum of 233 mJ of Erbium:YAG laser energy per pulse at a repetition rate of 10 Hz, and with fiber attenuation of only ~ 1 dB/m, more than sufficient for our medical application (Task 2 Improved).

REPORTABLE OUTCOMES

Manuscripts

1. Levin K, Tran D, Tchapijnikov A, **Fried NM**. Specialty fiber expands infrared laser applications. <u>Biophotonics International</u> 11(4):41-43, 2004. (cover article)

2. **Fried NM**, Yang Y, Chaney CA, Fried D. Transmission of Q-switched Erbium:YSGG and Erbium:YAG laser radiation through germanium oxide and sapphire optical fibers at high pulse energies. <u>Lasers in Medical Science</u> 19(3):155-160, 2004.

3. Varkarakis IM, Inagaki T, Allaf ME, Chan TY, Rogers CG, Wright EJ, **Fried NM**. Comparison of Erbium:YAG and Holmium:YAG lasers for incision of the urethra and bladder neck in a chronic porcine model. <u>Urology</u> 65(1):191-195, 2005.

4. **Fried NM**, Yang Y, Lee K, Tafti HA. Transmission of free-running and Q-switched Er:YAG laser energy through germanium / silica fibers. Proc. SPIE. In press.

5. Varkarakis IM, Inagaki T, Allaf ME, Chan TY, Rogers CG, Wright EJ, **Fried NM**. Erbium vs. Holmium laser incision of urethra and bladder neck. Proc. SPIE. In press.

Abstracts

1. **Fried NM**, Yang Y, Chaney CA. Comparison of sapphire and germanium oxide optical fibers for transmission of Q-switched and long-pulse ErbiumYSGG and Erbium:YAG laser radiation. <u>Journal of Endourology</u> 18(7):696-697, 2004.

2. Varkarakis IM, Inagaki T, Allaf ME, Rogers CG, **Fried NM**. Comparison of Erbium:YAG ($\lambda =$ 2.94 μm) and Holmium:YAG ($\lambda = 2.12$ μm) lasers for incision of the urethra and bladder neck: an in vivo chronic study in pigs. <u>Journal of Endourology</u> 18(7):698-699, 2004. *[2nd place, best poster competition in basic science, Engineering and Urology Society Meeting, San Francisco, CA, May 2004.]*

CONCLUSIONS

In the second year of this research project, we accomplished several aims. First, we demonstrated in an acute, *in vivo* pig model that the thermal damage zones measured only 20 ± 5 µm for the Erbium:YAG laser, comparable to previous *ex vivo* results of 10-20 µm, and much smaller than 660 ± 110 µm for Holmium:YAG laser. This result confirms our previous, *ex vivo*, studies reporting that the Erbium:YAG laser is 20-30 times more precise than the Holmium:YAG laser for incision of the urethra and bladder neck. We also performed short-term, chronic wound healing studies and discovered that there was 4 times less scarring after Erbium:YAG laser incision of healthy urethra and bladder neck as compared with the Holmium:YAG laser after 14 days. The Erbium:YAG laser incisions also healed twice as rapidly as Holmium:YAG laser incisions. For any given day of wound healing, there was less granulation tissue and smaller incision depth for Erbium:YAG laser than Holmium:YAG laser. We then worked on further improving the optical fiber delivery system for the Erbium laser. We characterized the hybrid fiber transmission rate, attenuation rate, and maximum pulse energy that the fiber can deliver for endoscopic applications in urology. The hybrid fiber was improved to deliver a maximum of 233 mJ of Erbium:YAG laser energy per pulse at a repetition rate of 10 Hz, and with fiber attenuation of only ~ 1 dB/m, more than sufficient for our medical application. In the third and final year of this research project, we perform longer term (28 days), chronic wound healing studies in pigs, comparing Erbium laser, Holmium laser, and cold knife incision of strictures.

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3. P. Albers, J. Fichtner, P. Bruhl, S. C. Muller, "Long-term results of internal urethrotomy," J. Urol., vol. 156, pp. 1611-1614, 1996.
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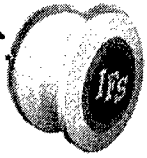
APPENDIX

Manuscripts

1. Levin K, Tran D, Tchapijnikov A, **Fried NM**. Specialty fiber expands infrared laser applications. <u>Biophotonics International</u> 11(4):41-43, 2004. (cover article)

2. **Fried NM**, Yang Y, Chaney CA, Fried D. Transmission of Q-switched Erbium:YSGG and Erbium:YAG laser radiation through germanium oxide and sapphire optical fibers at high pulse energies. <u>Lasers in Medical Science</u> 19(3):155-160, 2004.

3. Varkarakis IM, Inagaki T, Allaf ME, Chan TY, Rogers CG, Wright EJ, **Fried NM**. Comparison of Erbium:YAG and Holmium:YAG lasers for incision of the urethra and bladder neck in a chronic porcine model. <u>Urology</u> 65(1):191-195, 2005.

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5. Varkarakis IM, Inagaki T, Allaf ME, Chan TY, Rogers CG, Wright EJ, **Fried NM**. Erbium vs. Holmium laser incision of urethra and bladder neck. Proc. SPIE. In press.

Abstracts

1. **Fried NM**, Yang Y, Chaney CA. Comparison of sapphire and germanium oxide optical fibers for transmission of Q-switched and long-pulse ErbiumYSGG and Erbium:YAG laser radiation. <u>Journal of Endourology</u> 18(7):696-697, 2004.

2. Varkarakis IM, Inagaki T, Allaf ME, Rogers CG, **Fried NM**. Comparison of Erbium:YAG (λ = 2.94 μm) and Holmium:YAG (λ = 2.12 μm) lasers for incision of the urethra and bladder neck: an in vivo chronic study in pigs. <u>Journal of Endourology</u> 18(7):698-699, 2004. *[2nd place, best poster competition in basic science, Engineering and Urology Society Meeting, San Francisco, CA, May 2004.]*

Infrared Fibers for Laser Surgery

Ken Levin, PhD, Danh Tran, PhD and Alexei Tchapijnikov, Infrared Fiber Systems, Silver Spring, MD
Nathaniel Fried, PhD, Dept. of Urology, Johns Hopkins Medical School, Baltimore, MD

Lasers are currently being used extensively in medicine for therapeutic applications. Some examples of common therapeutic laser systems include the argon ion (green), excimer (ultraviolet), carbon dioxide (infrared), Neodymium:YAG (near-infrared), and Erbium:YAG (mid-infrared) lasers. The Er:YAG and Er:YSSG lasers are unique in that they operate close to the water absorption band at a wavelength of 2.9 microns, and are capable of precise tissue ablation at almost the cellular level with minimal thermal damage to adjacent healthy tissue. In addition, due to their high ablation efficiency, these laser systems can potentially be made compact at low cost. Erbium:YSGG and Erbium:YAG lasers are currently being used for a variety of medical applications in dermatology, dentistry, and ophthalmology. Their laser precision has proven beneficial for applications involving skin resurfacing, cavity preparation, and retinal surgery. Each of these medical applications has different requirements for the Erbium laser and optical fiber delivery system. Dental applications require high-power delivery to efficiently ablate hard tissues (e.g. dentin and enamel). Ophthalmic applications require precision laser surgery of delicate tissues with minimal thermal and mechanical damage to surrounding ocular structures. Cosmetic applications require both high-power and high-repetition-rate delivery of laser radiation for rapid skin resurfacing of large facial skin areas.

IR Fiber Delivery Systems

For lasers operating in the visible and near-infrared spectrum, conventional silica optical fibers can be used as a small, flexible, and inexpensive means of performing minimally invasive laser surgery via small openings in the body. However, for mid-infrared lasers such as the Er:YAG (2.94 µm) and Er:YSGG (2.79 µm), the laser radiation cannot be transmitted through conventional silica optical fibers due to the high absorption at these wavelengths. While for some Erbium medical applications, the use of a large, rigid articulated arm consisting of a series of rotating mirrors is sufficient, the use of a small, flexible optical fiber delivery system for delivery of mid-infrared laser radiation would be a significant improvement. There are a number of specialty IR fibers made from materials such as germanium oxide glass, fluoride glass, sapphire, as well as the hollow waveguide fiber.

Each of these fiber optic based delivery systems has its advantages and disadvantages. Fluoride glass fibers have the best transmission at 2.94 µm, but they are weak, moisture sensitive, can degrade with time, and generate toxic gases such as fluorine and hydrogen fluoride when damaged. Sapphire fiber is biocompatible and made of an extremely hard material which makes it perfect for reusable tips which come in direct contact with the tissue. However, sapphire is not the best choice for the long "trunk" fiber, because of its limited minimum bend radius and long-term mechanical degradation related to its crystalline structure. Sapphire fiber also has a relatively high absorption at 2.9 µm due to the lack of a core/clad structure. Hollow waveguides can handle power, but their transmission fluctuates greatly during actual use due to bending induced losses.

An infrared fiber based on germanium oxide glass has been optimized for use with mid-IR lasers such as Er:YSGG and Er:YAG. The germanium fiber has several advantages compared to other IR fibers. Germanium oxide is stronger, can handle more power, and is more chemically durable than fluoride fibers. Unlike the sapphire fiber and hollow waveguide, the germanium fiber has an optical cladding which minimizes bending losses. Fiber transmission losses are very low (less than 0.7 dB/meter at 2.94 microns and 0.25 dB/meter at 2.79 microns) with power handling over 20 watts for a 450-micron-core fiber (Figure 1).
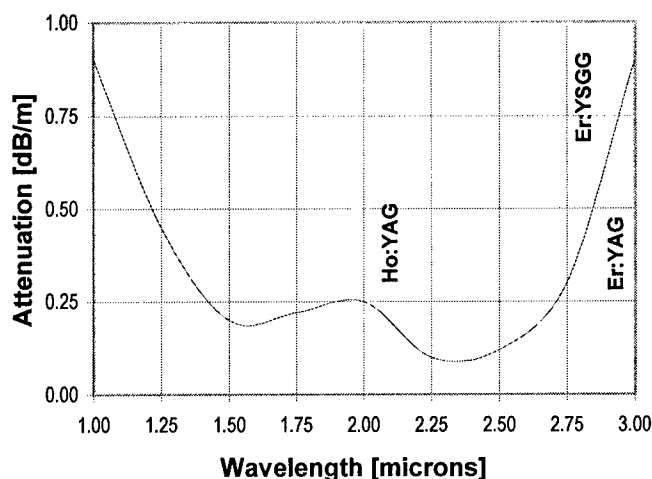
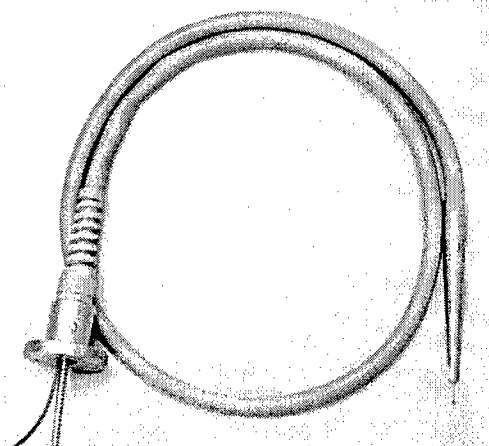**Figure 1.** Transmission loss of germanium fibers (from IFS).   **Figure 2.** Dental cable with handpiece

A typical delivery system for the Er:YAG laser consists of an approximately 2 meter long "trunk" fiber to deliver laser power from the laser system to the patient. The distal end of the fiber is attached to a probe terminated with a reusable or disposable tip made from sapphire or low-OH silica, and customized for the specific medical procedure of interest. Figure 2 shows one such delivery system being developed at IFS in conjunction with W&H Dentalwerk (Austria). This cable is designed to couple with different brands of Er:YAG lasers and features ease of alignment and robustness, as well as high power handling for different applications.

Er:YAG Laser Systems and Applications

There are currently a number of Er:YAG and Er:YSGG laser systems on the market, including dental lasers from Biolase and KaVo, aesthetic lasers from Asclepion Laser, Fotona and Sciton, and ophthalmic lasers from Austrian Laser and InPro. In addition, there are other lasers in the final stages of development.
In dentistry, the Er:YAG and Er:YSGG lasers have proven unique in their ability to cut dentin and enamel in a precise and char-free manner for applications such as cavity preparation and caries removal, usually without the need for anesthetic. These lasers are also being used in endodontics (sterilization and drying of the root canal), periodontics (closed curettage with removal of subgigival concrement), dental surgery (incisions and excisions, impacted wisdom teeth, removal of herpes), and tooth etching and sealing of fissures. The Er:YAG is being used in dermatology for skin resurfacing, removal of warts and lesions, hair removal, and the smoothing of scars, blemishes and wrinkles. Several ophthalmic applications are being investigated such as cataract removal, capsulorrhexis, capsulotomy, sclerostomy, and photorefractive keratotomy (PRK).

Er:YAG and Er:YSGG lasers with a flexible fiber optic delivery system have high potential in medical fields such as dentistry, ophthalmology, ENT, orthopedics, urology, and general surgery. Some of these applications, as mentioned above, are already on the market while others are at the stage of intensive development in research centers all over the world. The realization of a robust and reliable infrared fiber, such as the germanium oxide fiber, has played an important role in the establishment of the market for Er:YAG medical lasers and has stimulated study on new medical procedures and laser types. For example, Dr. Detlef Russ at the Institut für Lasertechnologien in der Medizin und Medtechnik (University of Ulm), in conjunction with Dornier MedTech, is investigating the use of an Er:YAG laser for the surgical treatment of carpal-tunnel syndrome [1]. They have developed a new surgical procedure to decrease the recurrence rate using the laser as a dissection tool for the carpal ligament by ablating a small amount of the carpal ligament and denaturing its ends. The laser energy was transmitted via a germanium oxide glass fiber. With this system they performed 11 carpal ligament dissections (Figure 3) without any complications in the follow-up period, and all patients were free of pain and recurrence.
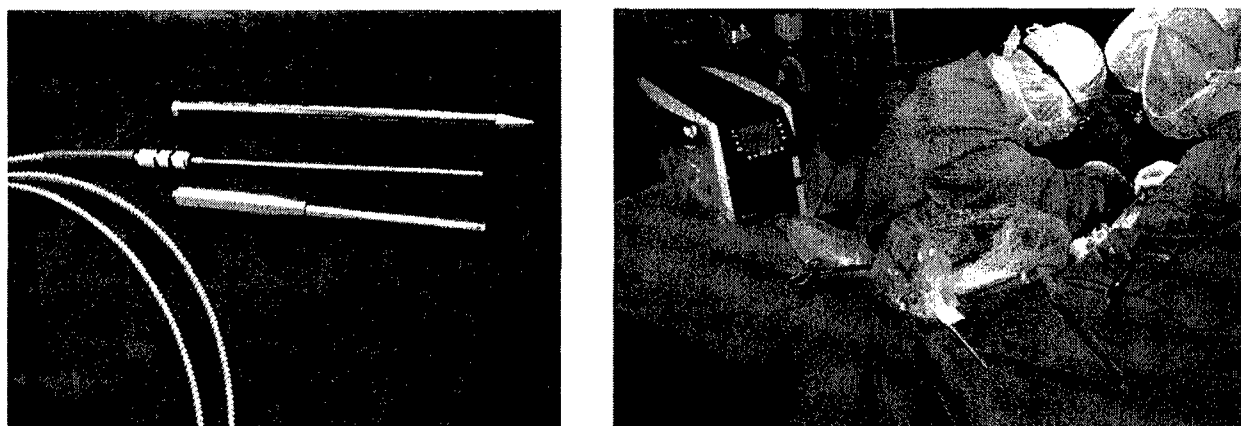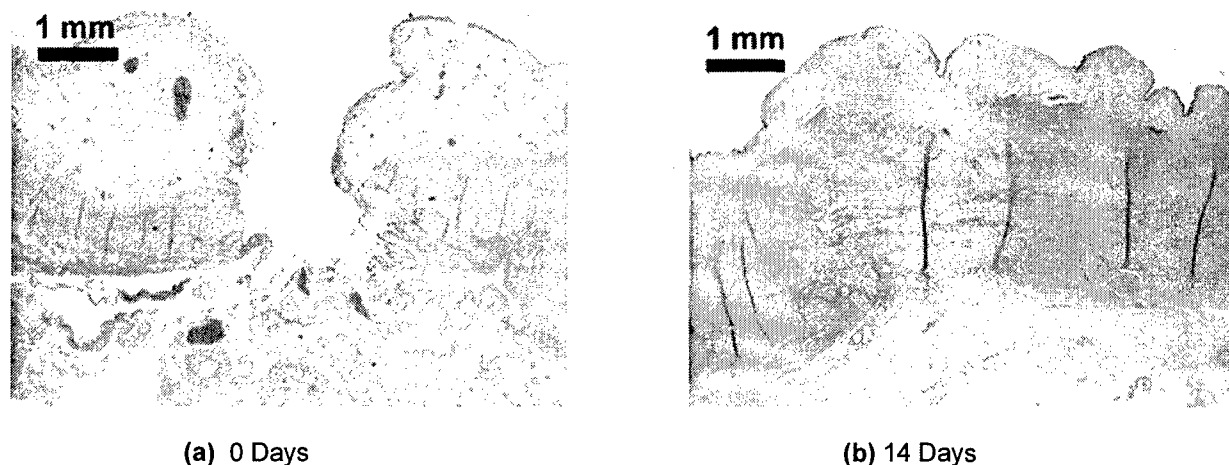
Figure 3. Left - the shielded fiber and sterilizable handpiece. Right – carpal surgery being performed.

Also at the University of Ulm, Dr. R. Hibst has used the Er:YAG laser for ENT surgery. Beginning in 1989, the benefit of different lasers for tympasnoplasty and stapedotomy (middle ear surgery) was investigated. It was demonstrated that the Er:YAG laser was optimum for operating on the ear drum, along the ossicles as far as the footplate without carbonization, and with sharp-edged canals "drilled" through the bone with a diameter of 0.2 mm [2]. Using this technique, children with mucotympanon could potentially have their eardrum reopened in the office without the need for draintubes.

Initial experimental studies conducted in collaboration with the Johns Hopkins Medical School also show that "hybrid" optical fibers consisting of a germanium trunk fiber and a low-OH silica tip are capable of transmitting up to 180 mJ of Er:YAG laser for potential medical applications requiring contact tissue ablation through a flexible endoscope [3]. This pulse energy is more than sufficient for ablation of a variety of both hard and soft tissues.

In urology, the germanium fibers are being tested for use with flexible endoscopes for precise Er:YAG laser incision of urethral, bladder neck, and ureteral strictures, and fragmentation of kidney stones [3,4]. The Er:YAG laser is approximately 10-20 times more precise for soft tissue ablation than the Holmium:YAG laser ($\lambda = 2.12$ µm), which is currently the laser of choice in urology. Figure 4 shows the wound healing results at Day 0 and Day 15, after precise incision of the bladder neck performed in a pig with the Er:YAG laser. Bladder neck strictures are defined as a narrowing or stenosis of the bladder neck which may result in recalcitrant scarring and urinary incontinence. A significant number (5-20 %) of patients undergoing surgery for benign or malignant prostate cancer suffer from bladder neck strictures, and there is currently not a simple and effective minimally invasive method of treatment.

(a) 0 Days   (b) 14 Days

Figure 4. H&E stained histological cross-section of the pig bladder neck after incision with the free-running Er:YAG laser. (a) At Day 0, a clean incision is made with the Er:YAG laser with no significant thermal damage present. (b) At Day 15, the incision has almost completely healed, with only a narrow zone of scar tissue present.

20

Another promising application is the short-pulse, Q-switched Er:YAG laser for procedures requiring high precision, e.g. in dentistry and ophthalmology. Preliminary results obtained with Johns Hopkins demonstrate that over 40 mJ of 500 nsec pulses are capable of being transmitted through the germanium oxide fiber [5]. Although fiber transmission losses are greater in Q-switched mode (Figure 5), this laser energy should also be sufficient for ablation of both hard and soft tissues. Delivery of Erbium laser radiation in a short-pulse, Q-switched mode may be important because it results in greater precision compared to the free-running Er:YAG. For example, the free-running Er:YAG laser with a pulse length of approximately 300 μs typically produces 10-50 μm of thermal damage in tissue, while short-pulse, Q-switched laser pulses of 500 ns duration reduces the thermal damage zone to only 5-10 μm resulting in improved precision during tissue ablation. Currently, the germanium fiber is being optimized for transmission of higher power in both short-pulse mode and for use with the hybrid fibers in the free-running mode.
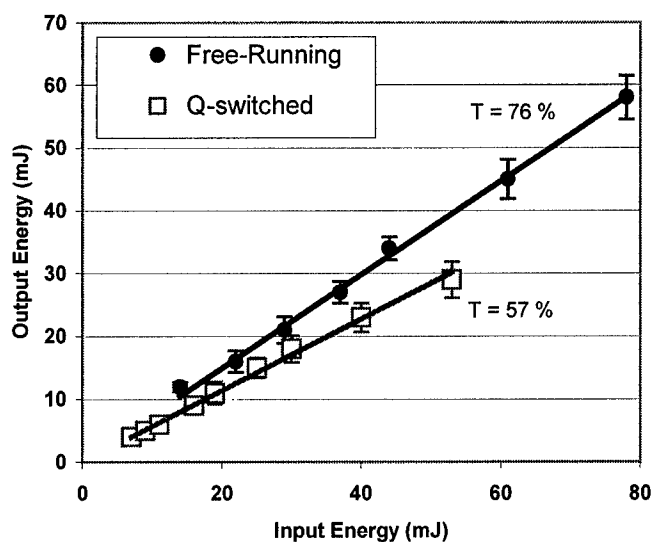
Conclusions

The availability of a reliable, low loss, chemically durable and high damage threshold fiber for delivery of mid-infrared laser radiation has made possible the widespread use of these lasers in a variety of medical and dental areas. These applications are expected to increase in the future as new procedures are investigated by the medical community. Improvements in fiber strength have allowed the use of the Er:YAG laser in procedures, such as invasive surgery, where tight fiber bending is required. Further improvements in fiber power handling will allow for even higher-power applications especially for Q-switched Er:YAG and Er:YSGG lasers.

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Figure 5. Percent transmission (T) of free-running (300 μs) and Q-switched (500 ns) Erbium:YSGG laser pulses through 450-μm-core germanium oxide optical fibers of 1 meter length. Data points represent the mean ± S.D. (n = 7).

Transmission of Free-Running and Q-switched Er:YAG and Er:YSGG Laser Energy Through Germanium Oxide / Silica Fibers

Nathaniel M. Fried[a*], Yubing Yang[a], Kyunhee Lee[b], Hussain A. Tafti[a]

[a] Dept. of Urology, Johns Hopkins Medical Institutions, Baltimore, MD
[b] Dept. of Biomedical Engineering, Johns Hopkins University, Baltimore, MD

ABSTRACT

Endoscopic Erbium laser applications have been limited by the lack of a suitable optical fiber. This study describes a hybrid germanium oxide / silica fiber for transmission of Q-switched and free-running Er:YAG and Er:YSGG laser radiation. Hybrid fibers consisted of a 1-meter-long germanium trunk fiber connected to a 1-cm-long silica fiber tip using PTFE, PET, or PTFE/FEP heat-shrink tubing. Maximum transmission of Er:YAG energy through fiber trunk/tip diameters of 250/365, 350/365, and 450/550 μm were recorded. The transmission rates through 450/550 μm fibers using Q-switched (500 ns) and free-running (300 μs) Er:YAG and Er:YSGG laser pulses were also measured. Maximum free-running Er:YAG pulse energies (fluences) measured up to 103 mJ (98 J/cm^2), 112 mJ (107 J/cm^2), and 233 mJ (98 J/cm^2), respectively, through 250/365, 350/365, and 450/550 hybrid fibers. Free-running Er:YAG and Er:YSGG transmission averaged 56% and 65%, with an attenuation of 1.1 ± 0.1 dB/m and 0.6 ± 0.1 dB/m, respectively, after correction for Fresnel losses (n = 7). Q-switched Er:YAG and Er:YSGG laser transmission averaged 55% and 62%, with an attenuation of 1.1 ± 0.2 dB/m and 0.9 ± 0.3 dB/m, respectively. Both Q-switched lasers transmitted a maximum pulse energy of 13 mJ (n = 7). The germanium / silica fiber is promising for use with the Erbium laser in applications requiring contact laser tissue ablation through a flexible endoscope.

Keywords: erbium, Q-switched, germanium, hybrid, mid-IR, fiber, oxide glass

1. INTRODUCTION

The Er:YAG ($\lambda = 2.94$ μm) and Er:YSGG ($\lambda = 2.79$ μm) lasers are used in dermatology and dentistry for precise tissue ablation. Recent urology studies have also shown that the Er:YAG laser is more precise for incision of soft urological tissues and more efficient for ablation of urinary stones than the Ho:YAG laser ($\lambda = 2.12$ μm), due to the increased water absorption near 3 μm [1-3]. However, Er:YAG laser applications in endoscopy are limited due to the lack of a suitable optical fiber. Several mid-infrared fibers are available, including chalcogenide, zirconium fluoride, sapphire, germanium oxide, and hollow silica waveguides. All of these optical waveguides have major limitations, including limited power delivery, chemical degradation in fluid environments, limited flexibility, low melting temperatures, tissue toxicity, and high cost [4,5]. The ideal mid-infrared fiber for use in endoscopic tissue ablation would combine high-power delivery, chemical and mechanical durability, flexibility and biocompatibility.

Previous preliminary studies in our laboratory have demonstrated that a hybrid fiber consisting of a germanium oxide trunk fiber and a silica fiber tip may be promising for use in endoscopic Erbium laser tissue ablation in contact mode [6-8]. The germanium trunk fiber is capable of delivering high Erbium laser pulse energies, and it is also sufficiently flexible to be inserted into most flexible endoscopes. The main limitation of the germanium fiber is its low melting temperature (~ 680 °C), which prevents its use for tissue ablation in contact mode. However, attachment of a robust and biocompatible low-OH silica tip with a higher melting temperature (~ 1175 °C) to the germanium fiber may allow for contact tissue ablation during endoscopic applications without fiber tip damage. During preliminary studies, the germanium fiber tip damage threshold during contact tissue ablation was increased significantly from 9 mJ without silica tip to 180 ± 30 mJ with the silica tip [6].

This study describes the high-power transmission properties of a hybrid germanium / silica optical fiber for potential use in endoscopic surgery. The hybrid fiber design was optimized, energy transmission was maximized, and transmission rates for Q-switched and free-running Er:YAG and Er:YSGG laser pulses were measured.

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*nfried@jhmi.edu; phone: 1 410 550 7906; fax: 1 410 550 3341

2. MATERIALS AND METHODS

A Schwartz Electro-Optics SEO 1-2-3 laser, operated with either an Er:YSGG (λ = 2.79 μm) or an Er:YAG (λ = 2.94 μm) laser rod, was used for the experiments. The laser was operated in free-running mode with a 300 μs pulse length and in short-pulse mode with a 500 ns pulse length produced by a rotating mirror Q-switch. The Q-switched Er:YAG and Er:YSGG laser pulse energy measured 25 mJ at 3 Hz. The laser pulse energy was measured using a Molectron EPM 1000 pyroelectric detector and the temporal pulse length was measured using a Boston Electronics PD-10.6 photovoltaic infrared detector. The laser radiation was focused with a 20-mm-focal-length calcium fluoride lens into hybrid germanium / silica optical fibers consisting of a 1-meter-length germanium oxide trunk fiber (Infrared Fiber Systems, Silver Spring, MD) with a 1-cm-length low-OH silica fiber tip. The trunk/tip fiber-core diameters measured 250/365, 350/365, and 450/550 μm and were attached with three different types of heat-shrink tubing: (a) PTFE, (b) PET, and (c) PTFE / FEP combination (Table 1, Figure 1). A linear fit to the data points provided the average percent transmission of the fibers, which was then corrected by subtracting the Fresnel losses, and the attenuation calculated in dB/m. The data points for each graph represent the average of 7 independent measurements from 7 different fibers, and the error bars represent the minimum and maximum values recorded.

Table 1. Heat-shrink tubing materials used to connect hybrid fibers.

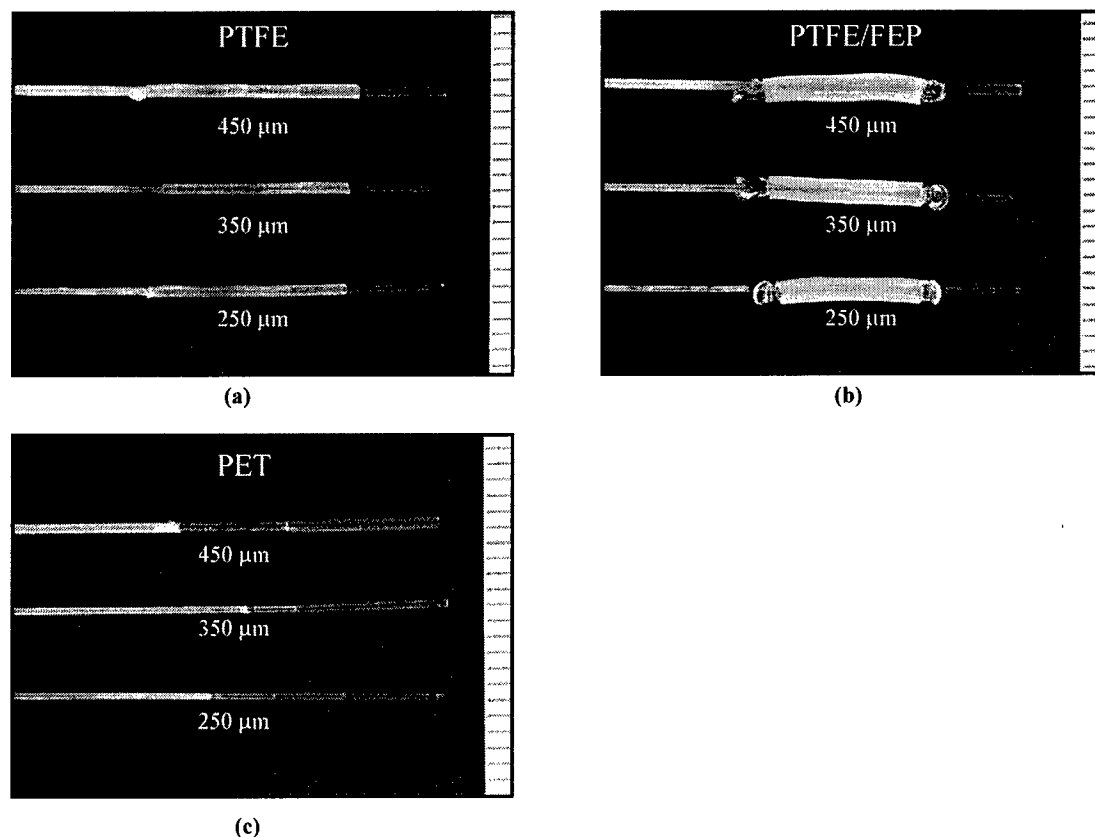| Material	Pre-/Post-Shrink ID (μm)	Wall Thickness (μm)	Shrink Temp. (°C)
PTFE	850 / 375	150	343
PTFE / FEP	900 / 0	575	343 / 17
PET	350 / 280	12.5	85-190
	450 / 360	12.5	
	725 / 580	25	

(a)

(b)

(c)

Figure 1. Hybrid germanium/silica fibers assembled using: (a) PTFE; (b) PTFE / FEP; (c) PET. A 1-cm-long, silica tip was attached to a 1-m-long germanium fiber. Germanium fiber diameters are 450, 350, and 250 μm. Ruler bar = 1 mm increments.

3. RESULTS

3.1 Hybrid Fiber Assembly

PTFE was found to be the most reliable material producing the highest Er:YAG pulse energy transmission, although the high shrink temperature resulted in melting of the Hytrel coating on the germanium fiber (Figure 1a). The PTFE / FEP shrink-melt combination produced the worst results. The shrink pressure and melted FEP tended to push the silica tip away from the germanium trunk fiber, causing sub-optimal alignment at the fiber interface and resulting in poor laser transmission and low damage thresholds (Figure 1b). The major limitation of the PET tubing was its wall thickness (12.5 – 25 μm), which results in weak bending strength (Figure 1c). PET is also limited to only approximately 20% shrinkage, so the trunk and tip fiber outer diameters need to match more precisely than with PTFE. However, PET has some advantages: its low shrink temperature eliminates melting of the germanium Hytrel jacket, its transparency provides better alignment of the fiber interface, and it shrinks more uniformly than PTFE.

3.2 Peak Output Energies

Maximum hybrid fiber transmission of free-running Erbium:YAG laser radiation was measured with the silica tips placed in contact with human urinary stones ex vivo, in a saline bath (Table 2). The peak hybrid fiber transmission of Erbium:YAG laser energy was approximately 100 J/cm^2 for all of the fiber diameters (250/365, 350/365, 450/550) tested, with pulse energies reaching as high as 233 mJ at 10 Hz. Average fiber transmission measured approximately 70 J/cm^2 for these fiber diameters. Transmission of Q-switched Er:YAG laser energy was also measured through 450/550 hybrid fibers, with peak pulse energies of 13 mJ.

Table 2. Peak and average Er:YAG pulse energies transmitted through hybrid germanium / silica fibers.

Fiber Core (μm) (Trunk / Tip)	Maximum		Average	
	Energy (mJ)	Fluence (J/cm^2)	Energy (mJ)	Fluence (J/cm^2)
250 / 365	103	98	74 ± 29	71
350 / 365	112	107	79 ± 24	75
450 / 550	233	98	157 ± 46	66

3.3 Transmission and Attenuation Measurements

The percent transmission of free-running and Q-switched Er:YAG and Er:YSGG laser radiation through 1-meter-length germanium oxide trunk fibers with a 1-cm-length low-OH silica tip was measured (Figure 2). Transmission rates for the free-running Er:YAG and Er:YSGG lasers measured 56% and 65%, respectively (n = 7 fibers). After correction for the Fresnel reflection losses at the fiber interfaces, the fiber attenuation measured 1.1 ± 0.1 dB/m and 0.6 ± 0.1 dB/m, respectively. The transmission rate for the Q-switched Er:YAG and Er:YSGG lasers was 55% and 65%, with an attenuation of 1.1 ± 0.2 dB/m and 0.9 ± 0.3 dB/m, respectively. Both Q-switched lasers transmitted a maximum pulse energy of 13 mJ (n = 7 fibers).
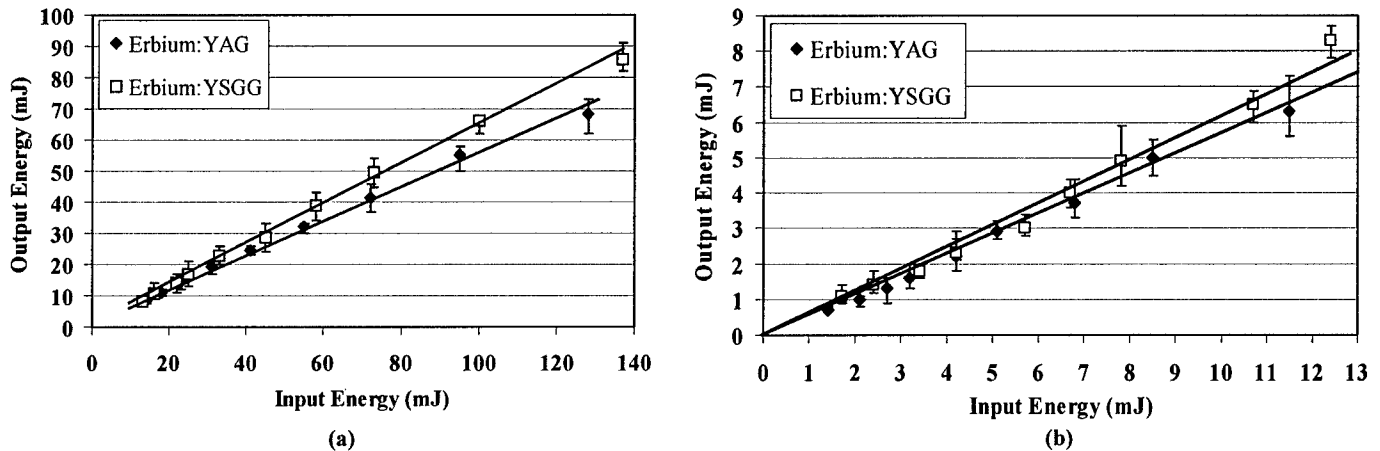

Figure 2. Hybrid fiber transmission rates for Er:YAG and Er:YSGG laser radiation during (a) free-running (300 μs) and (b) Q-switched (500 ns) operation. All fibers tested were 450 / 550 μm hybrid fibers.

4. DISCUSSION

In this study, we demonstrated a simple, biocompatible, and inexpensive method of assembling hybrid germanium / silica optical fibers using PTFE heat-shrink tubing. Peak hybrid fiber energies of up to 233 mJ at 10 Hz were transmitted through the fibers with the fluence reaching approximately 100 J/cm^2 for all the fiber diameters (250/365, 350/365, 450/550) tested. Although average pulse energies were lower and bending losses have previously been recorded [6], transmitted energies are still well above what is

necessary for Er:YAG laser ablation of most soft and hard tissues. For example, for soft tissues a low laser fluence of only 1-5 J/cm^2 is sufficient [9], while for hard tissues a higher laser fluence of 20-40 J/cm^2 may be necessary for efficient tissue ablation [10,11].

This study also demonstrated for the first time Q-switched transmission of Er:YAG and Er:YSGG laser radiation through the hybrid germanium / silica fibers. Q-switched delivery of Erbium laser energy provides an ultra-precise method of tissue ablation. For example, peripheral thermal damage caused in tissue during Er:YAG laser ablation may be reduced from 10-50 μm in the free-running mode to only 5-10 μm in Q-switched mode [9]. Previous studies have shown that Q-switched Er:YAG laser energy could be transmitted through germanium oxide fibers [12,13]. However, the Q-switched pulse energies of up to 13 mJ measured in this study are sufficient for ablation of soft tissues and demonstrate that delivery of Q-switched Er:YAG laser energy through a flexible, germanium oxide fiber in contact mode with tissue is feasible.

Not surprisingly, fiber attenuation was lower at the 2.79-μm Er:YSGG wavelength, due to lower OH⁻ absorption in the germanium and sapphire fibers than at the longer, 2.94-μm Er:YAG wavelength. Tables 3 and 4 provide a comparison of free-running and Q-switched Er:YAG and Er:YSGG laser fiber transmission and attenuation between the hybrid fibers and previous studies characterizing the bare germanium and sapphire fibers [13]. The attenuation through the hybrid fiber is significantly higher than that through the germanium and sapphire fibers. This is most likely due to coupling losses at the germanium / silica interface as well as the high attenuation through the silica tip. However, considering the relatively low pulse energies necessary to ablate tissue (a few mJ), the availability of high-power Erbium lasers (Joules/pulse), and the need for only a few meters of fiber length for most medical applications, a fiber attenuation of 0.6 – 1.1 dB/m is more than adequate.

Table 3. Percent transmission of Er:YAG and Er:YSGG laser radiation through mid-IR fibers.

Fiber Type	Er:YSGG ($\lambda = 2.79$ μm)		Er:YAG ($\lambda = 2.94$ μm)	
	Free-running	Q-switched	Free-running	Q-switched
Sapphire	88 ± 6	65 ± 3	77 ± 5	74 ± 4
Germanium	76 ± 2	57 ± 1	68 ± 2	64 ± 6
Hybrid	65 ± 2	62 ± 5	56 ± 3	55 ± 4

Table 4. Attenuation (dB/m) of Er:YAG and Er:YSGG laser radiation through mid-IR fibers.

Fiber Type	Er:YSGG ($\lambda = 2.79$ μm)		Er:YAG ($\lambda = 2.94$ μm)	
	Free-running	Q-switched	Free-running	Q-switched
Sapphire	0.2 ± 0.1	1.0 ± 0.2	0.4 ± 0.2	0.6 ± 0.2
Germanium	0.3 ± 0.1	1.3 ± 0.1	0.7 ± 0.1	0.9 ± 0.3
Hybrid	0.6 ± 0.1	0.9 ± 0.3	1.1 ± 0.1	1.1 ± 0.2

5. CONCLUSIONS

A novel, hybrid germanium oxide / silica optical fiber was optimized for the delivery of free-running and Q-switched Er:YAG and Er:YSGG laser radiation. Peak fiber transmission and attenuation was measured. Sufficient Erbium laser energy was transmitted for potential use in both hard and soft tissue ablation. This optical fiber may be useful in endoscopic medical applications requiring a flexible fiber for contact tissue ablation.

ACKNOWLEDGMENTS

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Erbium vs. Holmium Laser Incision of the Urethra and Bladder Neck

Ioannis M. Varkarakis[a], Takeshi Inagaki[a], Mohamad E. Allaf[a], Theresa Y. Chan[a,b], Craig G. Rogers[a],
E. James Wright[a], Nathaniel M. Fried[a*]

Depts. of Urology[a] and Pathology[b], Johns Hopkins Medical Institutions, Baltimore, MD

ABSTRACT

The objective of this study is to evaluate in an animal model differences in wound healing and scar formation in healthy urethra and bladder neck incised with the Erbium:YAG and Holmium:YAG lasers. In each of 18 domestic pigs, three 1-cm-long incisions were made, two at the bladder neck and one in the mid-urethra using either the Er:YAG laser (9 pigs) or the Ho:YAG laser (9 pigs). In each laser group, three animals were sacrificed on postoperative (POD) days 0, 6, and 14. Width of collateral damage, as evidenced by coagulation necrosis and granulation tissue at the wound base, and incision depth were evaluated during tissue analysis. Collateral damage with the Er:YAG laser at POD 0, 6 and 14 was 20 ± 5 μm, 900 ± 100 μm, and 430 ± 100 μm, respectively. Damage with the Ho:YAG laser was 660 ± 110 μm, 2280 ± 700 μm, and 1580 ± 250 μm, respectively. The granulation tissue was significantly less ($p < 0.05$) at all time points with the Er:YAG laser. Similarly, incision depths for the two laser groups at days 6 (1100 ± 200 μm vs 1500 ± 300 μm) and 14 (670 ± 140 μm vs 1240 ± 140 μm) were also significantly less ($p < 0.05$) for the Er:YAG laser group, indicating faster healing of the wound created. In this in vivo animal study, incisions in the urethra and bladder neck made with the Er:YAG laser healed faster and with less scar formation than incisions made with the Ho:YAG laser.

Key Words: urethra, bladder neck, laser, erbium, holmium, incision, stricture

1. INTRODUCTION

The management of urethral strictures is challenging because of their tendency to recur. Minimally invasive techniques (e.g. balloon dilatation and cold knife incision) have been used as an alternative to surgical reconstruction, but and have widely variable success rates ranging from 20-80% [1-3]. During internal urethrotomy, the scarred epithelium is separated and healing occurs by secondary intention. Epithelialization progresses from the wound edges, while at the same time wound contracture ensues. If wound contraction significantly narrows the urethral lumen before completion of epithelialization, stricture recurrence occurs. The race between these two phenomena is difficult to modify [4]. A vicious cycle between incision of the stricture and new scar formation from injury caused during therapy is a potential mechanism responsible for these failures.

A variety of lasers, including CO_2 [5] argon [6], Nd:YAG [7,8] KTP [9] and Ho:YAG [10-12] have been used to vaporize rather than incise the scar tissue, but they have had mixed results. These lasers produce significant thermal damage and necrosis, and they have proven to be no better than simple cold knife internal urethrotomy [5-13]. The ideal laser to use for urethral strictures and bladder neck contractures would be one that totally vaporizes the scar tissue, without causing collateral thermal damage. This should minimize postoperative scarring and result in higher success rates. In an acute animal model, the Er:YAG laser has been shown to be very precise, with a peripheral thermal damage zone of only 10-20 μm, compared to 300-400 μm seen with the Ho:YAG laser [14,15]. This large difference in collateral damage is due to the specific wavelength of the Er:YAG laser, which matches a major water absorption peak in tissue allowing it to be more strongly absorbed than the Ho:YAG laser.

The objective of this study is to evaluate in an animal model differences in wound healing and scar formation in healthy urethra and bladder neck incised with the Er:YAG and Ho:YAG lasers. The hypothesis evaluated is that decreased peripheral thermal damage caused by the Er:YAG laser will translate into more rapid wound healing and less scar formation compared to the Ho:YAG laser. This will potentially find an application in treating urethral strictures and bladder neck contractures, where minimal new scar formation is required to decrease recurrence rates.

*nfried@jhmi.edu; phone: 1 410 550 7906; fax: 1 410 550-3341

2. MATERIALS AND METHODS

2.1 Laser Parameters

An Er:YAG laser (SEO 1-2-3, Schwartz Electro-optics, Orlando, FL) operating at a wavelength of 2.94 μm, a pulse duration of 70 μs, fiber output pulse energy of 20 mJ, and repetition rate of 10 Hz was used. The laser radiation was focused into a 250-μm-core sapphire optical fiber (Photran, Amherst, NH). A Ho:YAG laser (SEO 1-2-3) operating at a wavelength of 2.12 μm, pulse duration of 300 μs, fiber output energy of 500 mJ, and repetition rate of 3 Hz, was also used. The laser radiation was focused into a 300-μm-core silica optical fiber (Table 1).

Table 1. Summary of laser parameters used in this study.

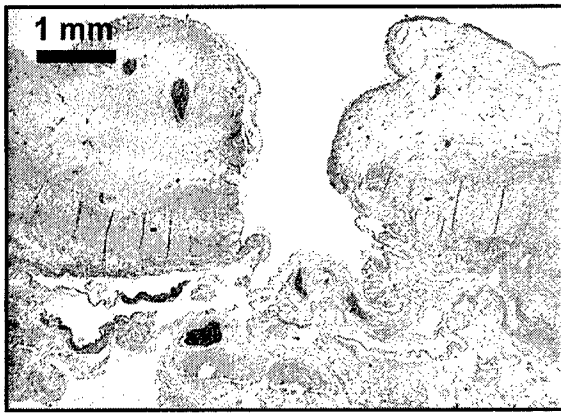| Laser Parameters	Holmium	Erbium
Wavelength (μm):	2.12	2.94
Energy / pulse (mJ):	500	20
Pulse Length (μs):	300	70
Pulse Repetition Rate (Hz):	3	10
Fiber Core Diameter (μm):	300	250
Fiber Type:	silica	sapphire

2.2 Animal Studies

All procedures were approved by the JHU Animal Review Committee (ACR# SW01M293). A total of 18 female pigs (30-45 kg) were divided into two arms, with 9 pigs in each laser arm. Three animals in each arm were sacrificed on postoperative days 0, 6, and 14. During the procedure, access to the urethra and bladder neck was obtained using a 17F rigid cystoscope with 30-degree lens. Three 1-cm-long incisions were made in each pig, two at the bladder neck and one in the mid-urethra. After the procedure a 14F urethral catheter was left in the bladder then removed after 3-4 hours. The pigs were euthanized, and the bladder and urethra samples were removed for histopathological processing. Quantitative measurements of collateral injury and incision depth were made. Collateral damage on day 0 was recorded as coagulative necrosis from the incision outward, while on days 6 and 14 as the extent of granulation width at the wound base. These parameters were analyzed using a Student's t-test.
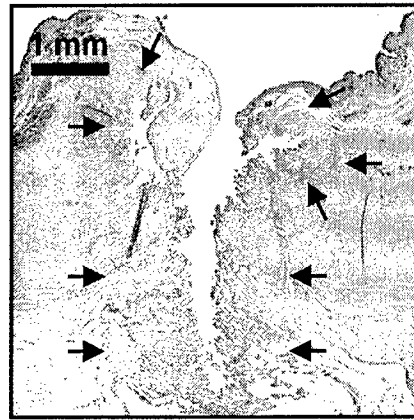
3. RESULTS

On day 0, Er:YAG and Ho:YAG laser incisions in the mid-urethra and bladder neck were of comparable depth, averaging 2540 ± 390 μm and 2530 ± 780 μm, respectively (p = 0.49) (Table 2). The zone of coagulative necrosis (Figure 1a-b) was significantly higher for the Ho:YAG laser than for the Er:YAG laser (660 ± 110 μm vs 20 ± 5 μm, respectively, p = 0.01). On day 6 (Figure 1c-d), the granulation tissue width at the incision base was 900 ± 100 μm and 2280 ± 700 μm, for the Er:YAG and Ho:YAG lasers, respectively (p = 0.04). After 14 days the granulation tissue created by the Er:YAG laser was less than the Ho:YAG laser (430 ± 100 μm vs 1580 ± 250 μm, respectively, p = 0.03) (Figure 1e-f). As wound healing progressed, granulation tissue filled the wound bed and decreased the incision depth. At day 6, the Er:YAG and Ho:YAG laser incisions were 45% and 60% of initial depth (1100 ± 200 μm vs 1500 ± 300 μm, respectively, p = 0.04). On day 14, the Er:YAG and Ho:YAG incisions were 25% and 50% of initial depth (670 ± 140 μm vs 1240 ± 140 μm), respectively (p = 0.02). Images of the tissue surface at 14 days also demonstrate accelerated wound healing after Er:YAG incision compared with Ho:YAG incision (Figure 2a-b).

Table 2. Injury parameters after incisions made with Ho:YAG and Er:YAG lasers at postoperative day 0, 6, and 14.
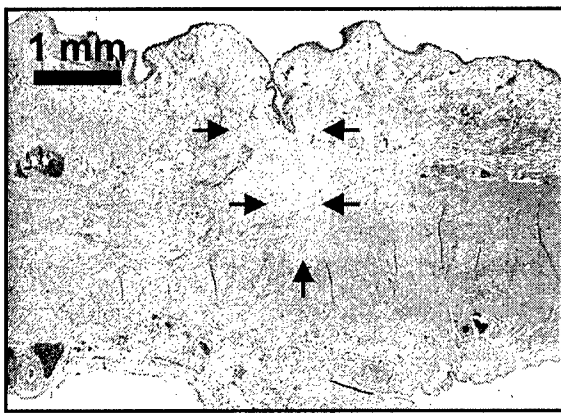
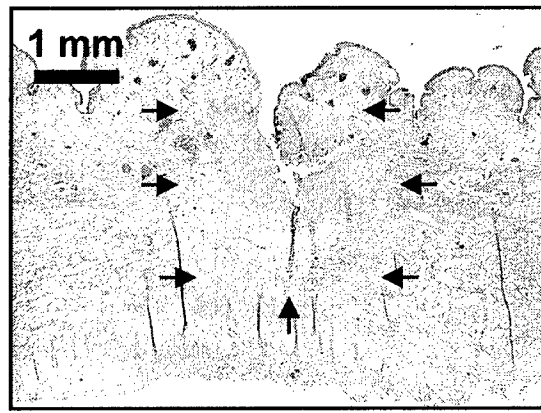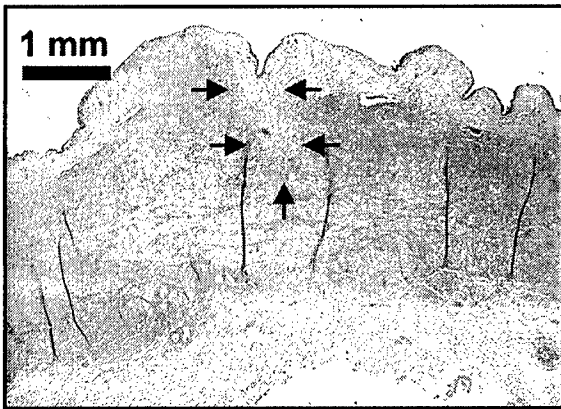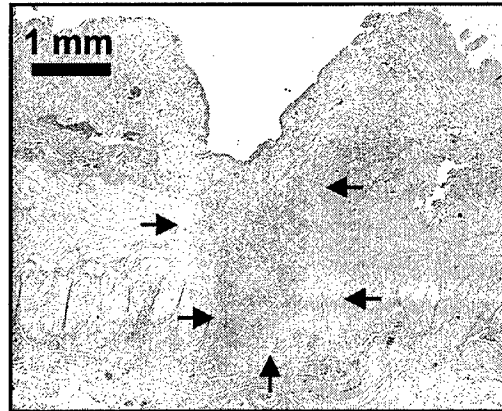| Laser	n	Day 0		n	Day 6		n	Day 14	
		Incision Depth (μm)	Thermal Damage (μm)		Incision Depth (μm)	Granulation Width (μm)		Incision Depth (μm)	Granulation Width (μm)
Holmium	3	2530 ± 780	660 ± 110	3	1500 ± 300	2280 ± 700	3	1240 ± 140	1580 ± 250
Erbium	3	2540 ± 390	20 ± 5	3	1100 ± 200	900 ± 100	3	670 ± 140	430 ± 100
P value		0.49	0.01		0.04	0.04		0.02	0.03

(a) Er:YAG, Day 0

(b) Ho:YAG, Day 0

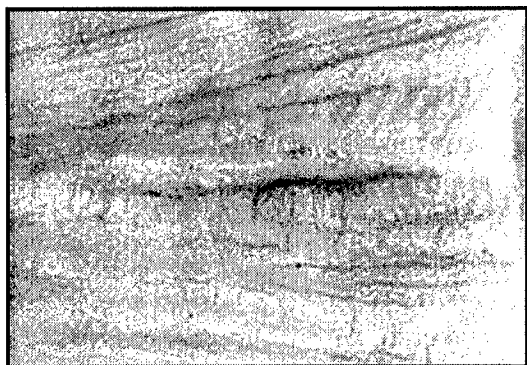**(c)** Er:YAG, Day 6

(d) Ho:YAG, Day 6
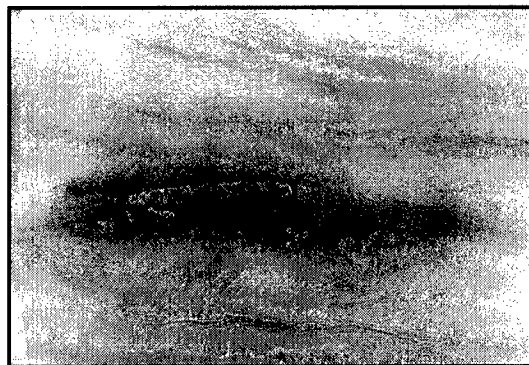
(e) Er:YAG, Day 14

(f) Ho:YAG, Day 14

Figure 1. H&E stained histologic cross-sections of incisions made with the Er:YAG and Ho:YAG laser on post-operative days 0, 6, and 14. Arrows demarcate the border between native tissue and thermally coagulated tissue.

(a) Er:YAG, Day 14   **(b)** Ho:YAG, Day 14

Figure 2. Images of the incisions made with the Er:YAG and Ho:YAG lasers at day 14. (a) Er:YAG; (b) Ho:YAG.

4. DISCUSSION

This study confirms the minimal collateral thermal damage caused acutely by the Er:YAG laser by gross and histologic examination. Histologic examination demonstrated that the Er:YAG laser produced approximately four times less scar tissue than the Ho:YAG laser. The granulation zone and incision depth were also less in the Er:YAG laser arm than in the Ho:YAG laser for a given POD. Incisions made with the Er:YAG laser healed twice as rapidly as those with the Ho:YAG laser. This difference was also observed with tissue examination prior to formalin fixation. Er:YAG laser incisions at day 14 were difficult to identify because of almost complete healing.

Although the Er:YAG laser is a promising new technology for potential clinical use in endourologic applications, the laser has several limitations. First, due to the precise cutting of the Er:YAG laser and the limited coagulation it produces, the Er:YAG laser is not recommended for applications requiring hemostasis. Bleeding was more pronounced during incisions with this laser, although this did not translate into any postoperative problems.

Second, low-OH silica optical fibers do not transmit in the mid-infrared spectrum and therefore cannot be used at the 2.94-μm Er:YAG wavelength. Therefore, mid-infrared optical fibers are necessary for use with the Er:YAG laser. Unfortunately, mid-IR fibers (e.g. sapphire, germanium oxide, zirconium fluoride, and hollow silica waveguides) have major limitations, including inferior mechanical and chemical durability, or they are inflexible, toxic in tissue, and expensive. Although the sapphire fibers used in this study are adequate for use with rigid endoscopes in the lower urinary tract, these fibers are not sufficiently flexible for use with flexible scopes in the upper urinary tract.

Finally, the results presented in this short-term animal wound healing study refer to the incision of healthy, and not scarred, urethral and bladder neck tissue. It is predicted that the reduced water content in scar tissue compared to healthy tissue would result in greater thermal damage and scar formation after both Er:YAG and Ho:YAG incision. However, since both lasers rely predominantly on water absorption for tissue ablation, the large differential in thermal damage and scar formation between the Er:YAG and Ho:YAG lasers reported in this study should remain.

5. CONCLUSIONS

Incisions created in the urethra and bladder neck of an animal model with the Er:YAG laser heal more rapidly and with less scar formation than incisions made with the Ho:YAG laser. Clinical studies are currently in development to evaluate use of the Er:YAG laser in the treatment of urethral strictures and bladder neck contractures.

ACKNOWLEDGMENTS

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Comparison of Sapphire and Germanium Oxide Optical Fibers for Transmission of Q-switched and Long-Pulse Erbium:YSGG and Erbium:YAG Laser Radiation

Nathaniel M. Fried, Yubing Yang, and Charles A. Chaney

Department of Urology, Johns Hopkins University, Baltimore, MD

INTRODUCTION: Sapphire and germanium oxide optical fibers are capable of endoscopic delivery of Erbium:YSGG (λ = 2.79 μm) and Erbium:YAG (λ = 2.94 μm) mid-infrared laser radiation for precision hard and soft tissue ablation applications in urology. The sapphire fibers are adequate for use in contact mode with tissue inside rigid endoscopes. The germanium oxide fibers can be used in flexible endoscopes, but not in contact mode. Additionally, previous reports have demonstrated that peripheral thermal damage caused in tissue during Er:YSGG and Er:YAG laser ablation may be reduced from 10-50 μm during conventional long-pulse, free-running mode to only 5-10 μm in short-pulse, Q-switched mode. The goal of this study is to compare the attenuation of Er:YSGG and Er:YAG laser radiation during transmission through sapphire and germanium fibers for both short- and long-pulse laser operation.

METHODS: Fiber transmission studies were conducted using both free-running (300 μs) and Q-switched (500 ns) Er:YSGG and Er:YAG laser pulses delivered at 3 Hz through 1-meter-length, 450-μm germanium oxide and 425-μm sapphire optical fibers.

RESULTS: Transmission of free-running Er:YSGG energy averaged 76% and 88% for the germanium and sapphire fibers (n = 7). Er:YAG transmission was 68% and 77%, respectively. Q-switched Er:YSGG laser transmission averaged 57% and 65% for the germanium and sapphire fibers (n = 7). Q-switched Er:YAG transmission was 64% and 74%, respectively. Q-switched Er:YSGG pulse energies up to 42 mJ were transmitted through some fibers. However, fiber tip damage was observed at input/output energies exceeding 40 mJ / 25 mJ (n = 2). Q-switched Er:YAG pulse energies greater than 15 mJ were transmitted through the fibers without any evidence of fiber tip damage.

CONCLUSION: Both germanium oxide and sapphire optical fibers are capable of transmitting sufficient free-running and Q-switched Er:YSGG and Er:YAG laser radiation for use in both hard and soft tissue ablation. The percent transmission through the sapphire fibers was higher than through the germanium fibers. The percent transmission was also higher for long-pulse operation of the laser than in Q-switched mode. These results demonstrate that fiber optic delivery of Q-switched Erbium laser energy for potential use in ultra-precise tissue ablation applications is feasible.

Comparison of Erbium:YAG (λ = 2.94 µm) and Holmium:YAG (λ = 2.1 µm) Lasers for Incision of the Urethra and Bladder Neck: An In Vivo Chronic Study in Pigs

Ioannis M. Varkarakis, Takeshi Inagaki, Mohamad E. Allaf,
Craig G. Rogers, and Nathaniel M. Fried

Department of Urology, Johns Hopkins University, Baltimore, MD

INTRODUCTION: Previous work has shown that the Erbium:YAG laser is 15-30 times more precise than the conventional Holmium:YAG laser for incision of soft urological tissues. The Er:YAG laser produces a peripheral thermal damage zone of only 10-20 µm in comparison with 300-400 µm for the Ho:YAG laser. The goal of this study is to determine whether decreased peripheral thermal damage to adjacent healthy tissue will translate into reduced scarring after laser incision of the urethra and bladder neck.

METHODS: A total of 18 domestic pigs underwent laser incision of the urethra and bladder neck. Incisions made with each of the lasers tested were of equal depth (approximately 2.5 mm). The pigs were divided into two arms depending on the type of laser used. In the first arm, incisions were made using the Er:YAG laser (wavelength of 2.94 µm, a pulse length of 70 µs, a fiber output energy of 20 mJ, and a pulse repetition rate of 10 Hz, coupled into a 250-µm-core sapphire optical fiber), while the second arm used the Ho:YAG laser (wavelength of 2.12 µm, a pulse duration of 300 µs, a fiber output energy of 500 mJ, and a pulse repetition rate of 3 Hz, coupled into a standard 300-µm-core silica optical fiber). A total of three, 1-cm incisions were made in each pig, two at the bladder neck and one in the mid-urethra. Three pigs in each arm were sacrificed on each of the following days: day of surgery, POD 6, and POD 14, and each laser group. Tissue was harvested and processed using standard histopathological techniques and H&E staining. Wound healing markers including incision depth, immediate thermal and mechanical damage, and width of granulation tissue were quantified during analysis of the tissue sections under light microscopy.

RESULTS: At day 0, no evidence of significant thermal damage was seen in the incisions created with the Er:YAG laser, while a lateral zone of damage measuring 660 ± 110 µm, characterized by tissue tearing and coagulation, was observable in the incisions made with the Ho:YAG laser. After 14 Days, the width of granulation tissue measured 430 ± 100 µm and 1580 ± 250 µm for the Er:YAG and Ho:YAG incisions, respectively ($P < 0.05$). The depth of healed incisions measured 665 ± 135 µm and 1237 ± 144 µm for the Er:YAG and Ho:YAG laser incisions, respectively ($P < 0.05$).

CONCLUSIONS: Er:YAG laser incisions healed and closed more rapidly and with less scar formation than incisions made with the Ho:YAG laser. The Er:YAG laser represents a promising tool for precise tissue incision and ablation, and warrants further study for potential clinical use in treating urethral and bladder neck strictures.

ORIGINAL ARTICLE

Nathaniel M. Fried · Yubing Yang · Charles A. Chaney
Daniel Fried

Transmission of Q-switched erbium:YSGG (λ=2.79 μm) and erbium: YAG (λ=2.94 μm) laser radiation through germanium oxide and sapphire optical fibres at high pulse energies

Abstract The erbium:YSGG and erbium:YAG lasers are used for tissue ablation in dermatology, dentistry and ophthalmology. The purpose of this study was to compare germanium oxide and sapphire optical fibres for transmission of sufficient Q-switched erbium laser pulse energies for potential use in both soft and hard tissue ablation applications. Fibre transmission studies were conducted with Q-switched (500 ns) Er:YSGG (λ=2.79 μm) and Er:YAG (λ=2.94 μm) laser pulses delivered at 3 Hz through 1-m-long, 450-μm germanium oxide and 425-μm sapphire optical fibres. Transmission of free-running (300 μs) Er:YSGG and Er:YAG laser pulses was also conducted for comparison. Each set of measurements was carried out on seven different sapphire or germanium fibres, and the data were then averaged. Fibre attenuation of Q-switched Er:YSGG laser energy measured 1.3 ± 0.1 dB/m and 1.0 ± 0.2 dB/m for the germanium and sapphire fibres, respectively. Attenuation of Q-switched Er:YAG laser energy measured 0.9 ± 0.3 dB/m and 0.6 ± 0.2 dB/m, respectively. A maximum Q-switched Er:YSGG pulse energy of 42 mJ (26–30 J/cm^2) was transmitted through the fibres. However, fibre tip damage was observed at energies exceeding 25 mJ (n=2). Both germanium oxide and sapphire optical fibres transmitted sufficient Q-switched Er:YSGG and Er:YAG laser radiation for use in both soft and hard tissue ablation. This is the first report of germanium and sapphire fibre optic transmission of Q-switched erbium laser energies of 25–42 mJ per pulse.

N. M. Fried (✉) · Y. Yang · C. A. Chaney
Department of Urology, Johns Hopkins Medical Institutions,
4940 Eastern Avenue, Building A,
Baltimore, Maryland, MD 21224, USA
E-mail: nfried@jhmi.edu
Tel.: +1-410-5507906
Fax: +1-410-5503341

D. Fried
Department of Restorative Dentistry, University of California,
San Francisco, California, USA

Introduction

The Q-switched erbium:YAG (λ=2.94 μm) and Er:YSGG (λ=2.79 μm) lasers have been studied experimentally for precision tissue ablation in several medical specialities, including ophthalmology [1–6] and dentistry [7–10]. Peripheral thermal damage caused in tissue during Er:YAG and Er:YSGG laser ablation may be reduced from 10 μm to 50 μm in the long-pulse, free-running mode to only 5–10 μm in the short-pulse, Q-switched mode [11]. The laser fluence necessary for rapid and efficient ablation of a variety of hard and soft tissues has been previously reported for the Q-switched Er:YAG and Er:YSGG lasers. For soft tissues, such as skin, cornea, and aorta, a laser fluence of 1–5 J/cm^2 is sufficient [11]. However, for hard tissues, such as bone, dentin, and enamel, a higher laser fluence of 20–40 J/cm^2 may be necessary, and studies have demonstrated that shorter laser pulses provide more efficient ablation with fewer thermal effects [8, 12].

The replacement of a large, rigid articulated arm with a small, flexible optical fibre could prove beneficial in medical applications, where operating space for access of surgical instruments is limited (e.g. ophthalmology and dentistry). Several mid-infrared optical fibre delivery systems are commercially available, with the most promising for erbium laser delivery being sapphire, germanium oxide, and hollow waveguides [13]. The sapphire [14–22] and germanium oxide [23–27] fibres have been studied extensively for transmission of free-running erbium laser pulses, but little work has been performed that demonstrates short-pulse, Q-switched transmission. Previous studies that demonstrated fibre transmission of Q-switched erbium laser radiation have been conducted at only relatively low pulse energies of

less than 10 mJ [23–27]. This pulse energy may be insufficient for certain medical applications, especially those involving hard tissue ablation (e.g. dentistry).

Preliminary studies in our laboratories have demonstrated increased fibre optic transmission of Q-switched erbium:YSGG laser radiation using germanium oxide and sapphire optical fibres [28, 29]. The purpose of this study is to compare germanium oxide and sapphire optical fibres of similar size and length for transmission of both free-running and Q-switched Er:YSGG and Er:YAG mid-infrared laser radiation at high pulse energies sufficient for both soft and hard tissue ablation.

Materials and methods

A Schwartz Electro-Optics SEO 1-2-3 laser, operated with either an erbium:YSGG ($\lambda = 2.79$ μm) or an erbium:YAG ($\lambda = 2.94$ μm) laser rod, was used for the experiments. The laser was operated in free-running mode with a pulse length of 300 μs and in short-pulse mode with a rotating mirror Q-switch (Shiva Laser, Los Angeles, Calif., USA) producing 500 ns pulse lengths (Fig. 1). The Q-switched laser produced Er:YSGG energies up to 60 mJ per pulse and Er:YAG energies up to 25 mJ per pulse, at a repetition rate of 3 Hz. A single-mode Gaussian laser spatial beam profile was used in all

Fig. 1 Temporal pulse profile for the **a** free-running and **b** Q-switched Er:YSGG laser

experiments. The laser pulse–pulse stability was within ±5% for the free-running mode and ±10% for the Q-switched mode operation. The laser pulse energy was measured with a pyroelectric detector (Molectron, Model EPM 1000, Portland, Ore., USA) and the temporal pulse length was measured with a photovoltaic infrared detector (PD-10.6, Boston Electronics, Brookline, Mass., USA).

The laser radiation was focused with a 50-mm focal length calcium fluoride lens into either 450-μm-core germanium oxide optical fibres (Infrared Fiber Systems, Silver Spring, Md., USA) or 425-μm-core sapphire fibres (Photran, Amherst, N.H., USA). The input end of the fibres was placed at the focal point of the lens with a laser spot diameter of 340 μm. All the sapphire and germanium fibres tested in this study measured 1 m in length. Light microscopy was used to examine the input ends of the germanium and sapphire fibre tips for evidence of damage after high power Q-switched erbium: YSGG laser transmission studies.

Fibre attenuation comparisons were made either between sapphire and germanium fibres, for a given laser and pulse length, or between the Er:YAG and Er:YSGG laser, for a given fibre and pulse length. A linear fit to the data points provided the average percent transmission of the fibres over the entire input energy range (including the losses due to Fresnel reflection). This percent transmission measurement was then corrected by subtraction of the Fresnel losses, and the attenuation was calculated in decibels per metre. Statistical analyses were performed with the paired Student's t-test. Differences were considered significant at a level of $P < 0.05$. The data points for each graph represent the average of seven independent measurements from seven different fibres, and the error bars represent the minimum and maximum values recorded.
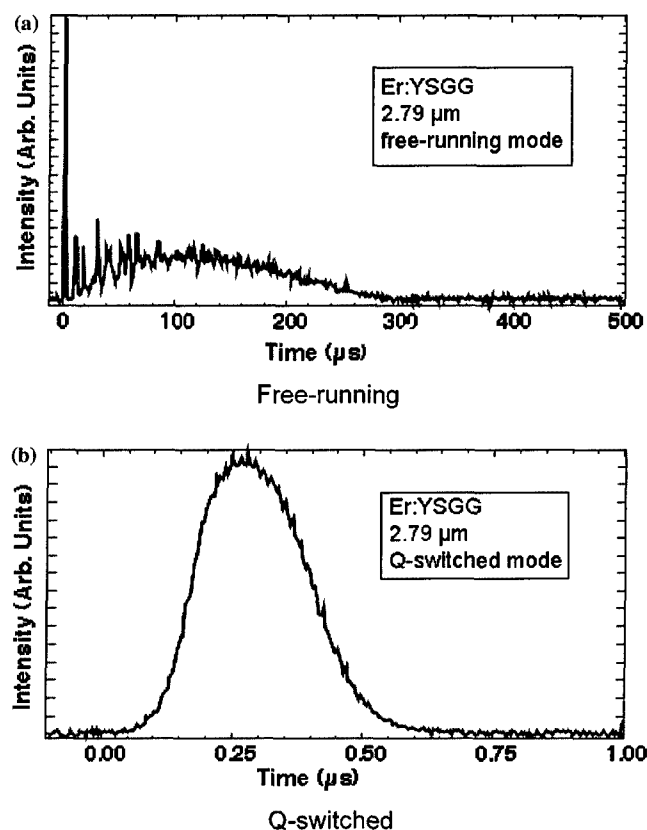
Results

Erbium:YSGG laser

The transmission of free-running and Q-switched Er:YSGG laser radiation through sapphire and germanium oxide optical fibres is shown in Fig. 2. Fibre optic transmission of free-running Er:YSGG laser radiation averaged 76 ± 2% and 88 ± 6% for the germanium and sapphire fibres ($n = 7$), respectively ($P < 0.05$). It should be noted that much of the loss was due not to transmission but, rather, to reflection at the fibre ends. Both the germanium and sapphire fibres have high indices of refraction. For sapphire the index of refraction is 1.71, which results in reflection losses of 6.9% at each end. The germanium fibre has an index of refraction of 1.84, which results in Fresnel losses of 8.7%, in comparison with only 4% reflection losses from silica fibres ($n_i = 1.4$) [13]. After correction for those Fresnel losses, attenuation through the germanium and sapphire fibres measured 0.3 ± 0.1 dB/m and 0.2 ± 0.1 dB/m, respectively.
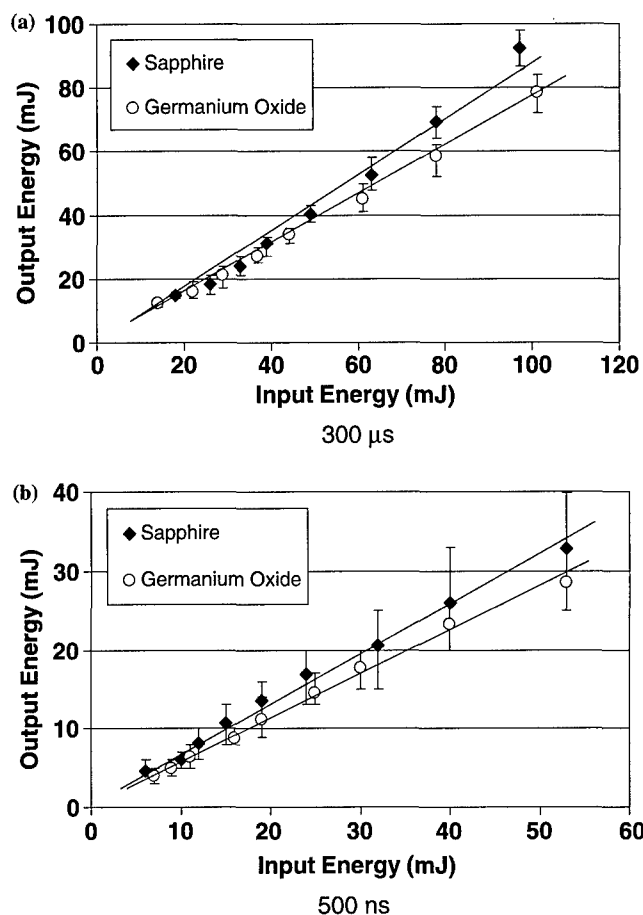
Fig. 2 Transmission of a free-running, 300-μs and b Q-switched, 500-ns Er:YSGG laser pulses through 1-m-long samples of 425-μm sapphire and 450-μm germanium oxide fibres at 3 Hz (seven fibres each)

Fig. 3 Transmission of a free-running, 300-μs and b Q-switched, 500-ns Er:YAG laser pulses through 1-m-long samples of 425-μm sapphire and 450-μm germanium oxide fibres at 3 Hz (seven fibres each)

Fibre optic transmission of Q-switched Er:YSGG laser radiation averaged $57 \pm 1\%$ and $65 \pm 3\%$ for the germanium and sapphire fibres $(n = 7)$, respectively $(P > 0.05)$. This corresponded to an attenuation of 1.3 ± 0.1 dB/m and 1.0 ± 0.2 dB/m, respectively. The Q-switched transmission was lower than free-running transmission, overall, for both the fibres, and the data exhibited more variability than the free-running data. This is most likely to be due to two factors. First, operation of the Er:YSGG laser in Q-switched mode resulted in greater pulse-to-pulse energy instability. Second, damage at the input end of several of the germanium $(n = 2)$ and sapphire $(n = 2)$ fibres was observed at Q-switched pulse energies above 40 mJ (input end) and 25 mJ (output end), respectively. Thus, at the higher energy levels (> 40 mJ input), permanent degradation and damage to the input end of the fibre might have occurred, affecting the transmission results. In at least one case a germanium oxide fibre also experienced catastrophic failure, as evidenced by a burning and snapping of the fibre jacket when the laser input energy was increased above 40 mJ. For both the free-running and Q-switched Er:YSGG lasers, the
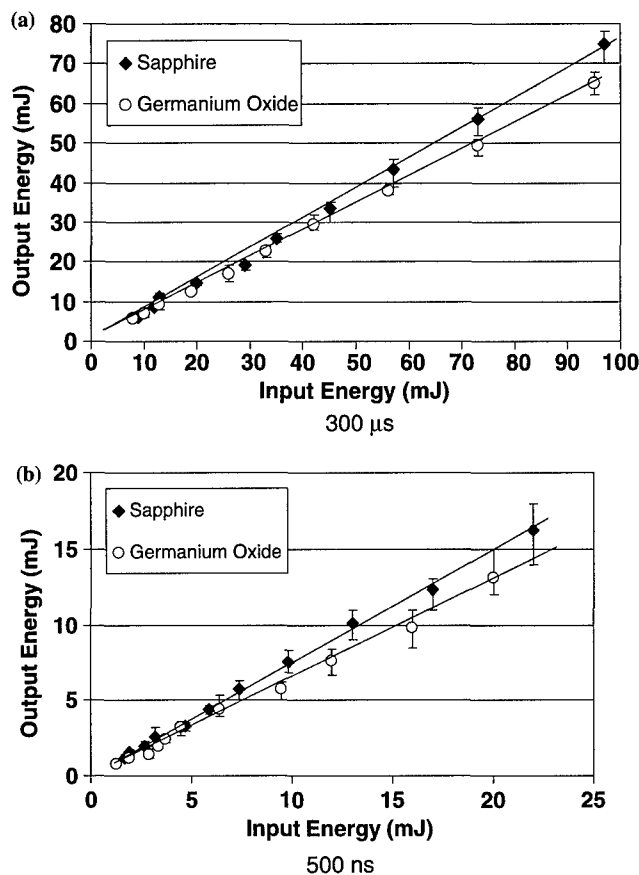
sapphire optical fibre had lower attenuation than the germanium fibre.

Erbium:YAG laser

The transmission of free-running and Q-switched Er:YAG laser radiation through sapphire and germanium oxide optical fibres is shown in Fig. 3. Fibre optic transmission of free-running Er:YAG laser radiation averaged $68 \pm 2\%$ and $77 \pm 5\%$ for the germanium and sapphire fibres $(n = 7)$, respectively $(P < 0.05)$. This corresponded to an attenuation of 0.7 ± 0.1 dB/m and 0.4 ± 0.2 dB/m, respectively. It is not a surprising result that the transmission of free-running Er:YSGG laser radiation is higher than that of the free-running Er:YAG laser. For example, the attenuation through germanium fibres is documented to be 0.7 dB/m for the Er:YAG and 0.3 dB/m for the Er:YSGG laser wavelengths [28]. This can be explained by the OH⁻ component in both the germanium and sapphire fibres, which is less absorbing at 2.79 μm than at 2.94 μm [19, 21].

Fibre optic transmission of Q-switched Er:YAG laser radiation averaged $64 \pm 6\%$ and $74 \pm 4\%$ for the ger-

Table 1 Transmission of Er:YSGG and Er:YAG laser radiation through 1-m-length germanium oxide and sapphire optical fibres

Laser	Peak pulse energy (mJ)		Percentage of transmission		Attenuation (dB/m)	
	Germanium	Sapphire	Germanium	Sapphire	Germanium	Sapphire
Er:YSGG						
Free-running	>2,000	>1,000	76±2	88±6	0.3±0.1	0.2±0.1
Q-switched	>25	>25	57±1	65±3	1.3±0.1	1.0±0.2
Er:YAG						
Free-running	>2,000 [28]	>1,000 [22]	68±2	77±5	0.7±0.1	0.4±0.2
Q-switched	>15	>15	64±6	74±4	0.9±0.3	0.6±0.2

manium and sapphire fibres ($n = 7$), respectively ($P < 0.05$). This corresponded to an attenuation of 0.9 ± 0.3 dB/m and 0.6 ± 0.2 dB/m, respectively. There was no evidence of fibre tip damage during these studies. However, it should be noted that the Q-switched Er:YAG laser output energy was limited to less than half that of the Q-switched Er:YSGG laser. The Q-switched transmission was lower than in free-running mode. However, it is unclear why the fibre attenuation of the Q-switched Er:YAG is lower than that of the Q-switched Er:YSGG. However, if the variability observed in the data at high Q-switched Er:YSGG laser energies is considered, there was no significant difference between the fibre optic transmission of Q-switched Er:YAG and Er:YSGG laser radiation ($P > 0.05$). A summary of the Q-switched erbium laser results for the fibre transmission studies is provided in Table 1. Previously reported free-running erbium laser pulse energies are also provided for comparison [22, 28].

Fibre tip damage

The input tips of the fibres damaged during the high-power transmission studies of Q-switched Er:YSGG laser pulses were examined by light microscopy. The germanium oxide fibre tips showed severe damage, characterised by chipping of the fibre tip (Fig. 4a). However, damage to the sapphire fibre tip was limited, to superficial damage characterised by a melting of the fibre tip surface (Fig. 4b). Damage to the input end of sapphire fibres during high-energy, long-pulse erbium laser fibre coupling has also been reported previously and was attributed to the melting of the fibre surface at high pulse energies [22].

Discussion

Previous studies by Papagiakoumou et al. and Serafetinides et al. (Athens, Greece) have reported the transmission of Q-switched and free-running Er:YAG laser radiation through a variety of mid-infrared delivery systems, including germanium oxide [23–25], sapphire [26, 27], and fluoride glass fibres [27, 30] and hollow waveguides [30]. Laser energies approaching 10 mJ of Q-switched Er:YAG laser radiation were successfully coupled into germanium fibres, with attenuation measuring only 0.60–0.75 dB/m, resulting in approximately 8 mJ per pulse transmission through the fibres [23–25].

The main purpose of this study was to build upon previous results by testing the Q-switched Er:YSGG and Er:YAG lasers with germanium and sapphire fibres at input energies significantly higher than 10 mJ, to demonstrate that sufficient Q-switched energy can be transmitted for both soft and hard tissue ablation. While less than 10 mJ is sufficient for soft tissue ablation, it might not be adequate for rapid and efficient ablation of hard tissues, as evidenced by previous reports of the ablation rates for bone and dental enamel [8, 12]. Higher incident fluence can be used on hard tissues before the onset of plasma shielding.
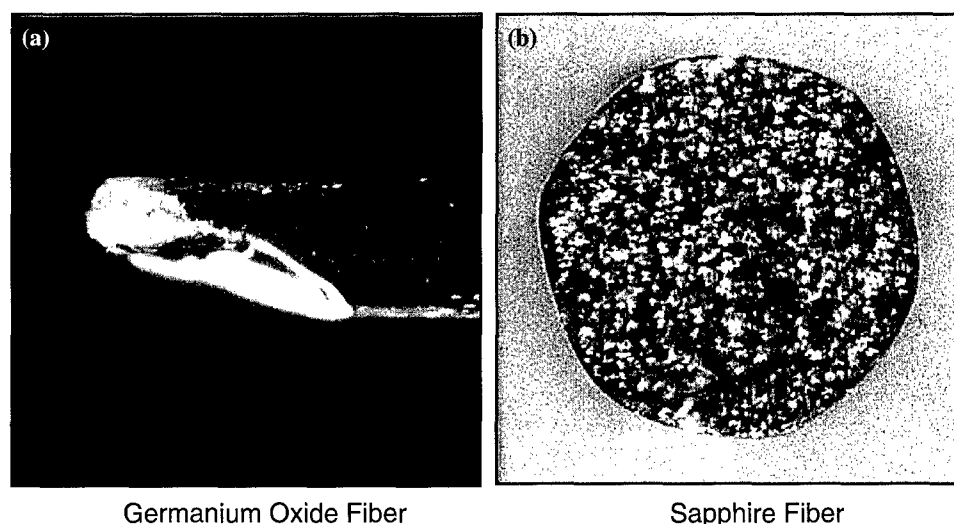
In this study we were able consistently to couple up to 40 mJ of Q-switched Er:YSGG laser energy into both the sapphire and germanium fibres without causing fibre damage, which resulted in fibre output energies of approximately 25 mJ per pulse. If the fibre is used in contact mode, this output energy translates into a fluence of 16–18 J/cm². Laser energies approaching 53 mJ were coupled into some of the fibres, with peak fibre outputs reaching up to 42 mJ per pulse (26–30 J/cm²).

We were limited by the lower laser output energy of the Q-switched Er:YAG laser. However, up to 22 mJ was coupled into the fibres, with peak fibre outputs reaching up to 18 mJ per pulse and no evidence of fibre tip damage. It is likely that even higher Q-switched Er:YAG pulse energies may be transmitted through germanium and sapphire fibres. However, the Q-switched Er:YAG laser used in this study was limited to output pulse energies of 25 mJ or less. In summary, the pulse energies and fluence transmitted through the fibres tested in these studies are sufficient for both soft and hard tissue ablation by Q-switched erbium laser.

Conclusions

Q-switched Er:YSGG laser pulse energies of 25 mJ per pulse were consistently transmitted through both sapphire and germanium oxide optical fibres ($n = 7$), with some fibres transmitting up to 42 mJ per pulse. These results represent a significant increase over previously reported results of less than 10 mJ per pulse and, thus, demonstrate that sufficient Q-switched erbium laser pulse

Fig. 4 Damage to the input fibre tip caused during high-power coupling of Er:YSGG laser pulses into the fibres. **a** Side view of the chipped germanium oxide fibre, **b** axial view of the melted sapphire optical fibre tip

Germanium Oxide Fiber

Sapphire Fiber

energy can be transmitted for rapid and efficient fibre optic ablation of a variety of both soft and hard tissues.

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COMPARISON OF ERBIUM:YTTRIUM-ALUMINUM-GARNET AND HOLMIUM:YTTRIUM-ALUMINUM-GARNET LASERS FOR INCISION OF URETHRA AND BLADDER NECK IN AN IN VIVO PORCINE MODEL

IOANNIS M. VARKARAKIS, TAKESHI INAGAKI, MOHAMAD E. ALLAF, THERESA Y. CHAN, CRAIG G. ROGERS, E. JAMES WRIGHT, AND NATHANIEL M. FRIED

ABSTRACT

Objectives. To evaluate, in an animal model, differences in wound healing and scar formation in healthy urethra and bladder neck incised with the erbium (Er):yttrium-aluminum-garnet (YAG) and holmium (Ho):YAG lasers.
Methods. In each of 18 domestic pigs, three 1-cm-long incisions were made, two at the bladder neck and one in the mid-urethra, using either the Er:YAG laser (9 pigs) or the Ho:YAG laser (9 pigs). In each laser group, 3 animals were killed on postoperative days 0, 6, and 14. The width of collateral damage, as evidenced by coagulation necrosis and granulation tissue at the wound base, and the incision depth were evaluated during tissue analysis.
Results. The collateral damage with the Er:YAG laser at postoperative day 0, 6, and 14 was 20 ± 5, 900 ± 100, and 430 ± 100 μm, respectively. The collateral damage with the Ho:YAG laser was 660 ± 110, 2280 ± 700, and 1580 ± 250 μm, respectively. The amount of granulation tissue was significantly less ($P < 0.05$) at all time points with the Er:YAG laser. Similarly, the incision depths for the Er:YAG and Ho:YAG laser at postoperative day 6 (1100 ± 200 μm versus 1500 ± 300 μm, respectively) and 14 (670 ± 140 μm versus 1240 ± 140 μm, respectively) were also significantly less ($P < 0.05$) for the Er:YAG laser group, indicating faster healing of the wound created.
Conclusions. In this in vivo animal study, incisions in the urethra and bladder neck made with the Er:YAG laser healed faster and with less scar formation than incisions made with the Ho:YAG laser. UROLOGY **65:** 191–195, 2005. © 2005 Elsevier Inc.

The management of urethral strictures is challenging because of their tendency to recur. Minimally invasive techniques have been used as an alternative to surgical reconstruction. Urethral balloon dilation and internal urethrotomy with cold knife incision are the most commonly used and have success rates ranging from 20% to 80%.[1-3] During internal urethrotomy, the scarred epithelium is separated and healing occurs by secondary intention. Epithelialization progresses from the wound edges, and at the same time wound contracture ensues. If wound contraction significantly narrows the urethral lumen before completion of epithelialization, stricture recurrence develops. The race between these two phenomena is difficult to modify.[4] A vicious circle between incision of the stricture and new scar formation from the injury caused by the therapy is a potential mechanism responsible for these failures.

In an effort to vaporize rather than incise scar tissue, laser energy from carbon dioxide,[5] argon,[6] neodymium:yttrium-aluminum-garnet (YAG),[7,8] potassium-titanyl-phosphate,[9] and holmium (Ho): YAG[10-12] has been used with mixed results. Each of these lasers produces significant thermal injury and necrosis, and the results have proved to be no better than those obtained with simple cold knife internal urethrotomy.[5-13]
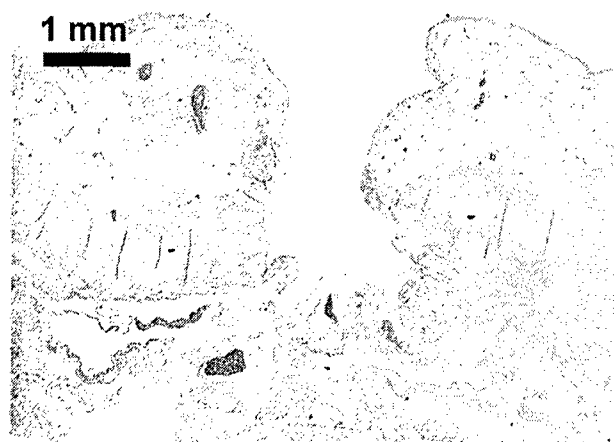
The ideal laser to use for urethral strictures and

A

B

FIGURE 1. *Hematoxylin-eosin-stained histologic cross-sections of incisions made with (A) Er:YAG and (B) Ho:YAG laser (arrows demarcate border between native and thermally coagulated tissue) on POD 0. No discernible thermal damage zone seen in tissue ablated with Er:YAG laser (A).*

bladder neck contractures would be one that totally vaporizes the scar tissue, without causing collateral thermal damage. This should minimize postoperative scarring and result in greater success rates. In an acute animal model, the erbium (Er): YAG laser has been shown to be very precise, with a peripheral thermal damage zone of only 10 to 20 μm, which is minimal compared with the thermal injury zone of 300 to 400 μm seen with the Ho: YAG laser.[14,15] This disparity in collateral damage is due to the specific wavelength (2.94 μm) of the Er:YAG laser, which closely matches a major water absorption peak in tissue, allowing it to be more

strongly absorbed than the Ho:YAG laser energy (wavelength of 2.12 μm).

The objective of this study was to evaluate, in an in vivo animal model, the differences in wound healing and scar formation in healthy urethra and bladder neck tissue incised with the Er:YAG and Ho:YAG lasers. The hypothesis evaluated was that the decreased peripheral thermal damage caused by the Er:YAG laser would translate into more rapid wound healing and less scar formation compared with that caused by the Ho:YAG laser. This could potentially find an application in treating urethral strictures and bladder neck contractures, for which minimal new scar formation is required to decrease the recurrence rates.

MATERIAL AND METHODS

LASER PARAMETERS

A scientific Er:YAG laser (SEO 1-2-3, Schwartz Electro-optics, Orlando, Fla), operating at a wavelength of 2.94 μm, produced a laser pulse duration of 70 μs, fiber output energy of 20 mJ per pulse, and a laser pulse repetition rate of 10 Hz. The laser radiation was focused with a 20-mm-focal-length calcium fluoride lens into a 250-μm-core, 2-m-long sapphire optical fiber (Photran, Amherst, NH).
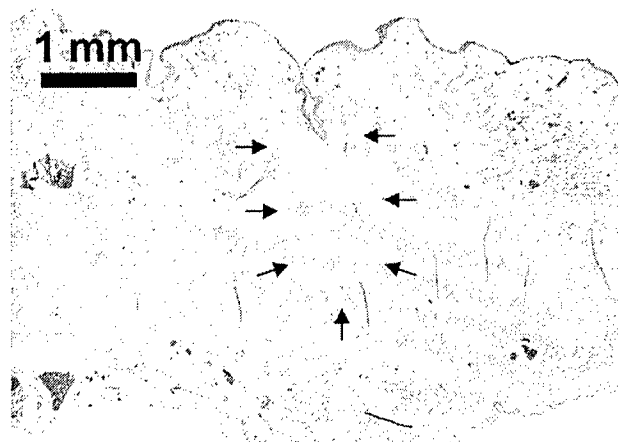
A scientific Ho:YAG laser (SEO 1-2-3, Schwartz Electro-optics), operating at a wavelength of 2.12 μm, laser pulse duration of 300 μs, fiber output energy of 500 mJ, and pulse repetition rate of 3 Hz, was also used. The laser radiation was focused into a 300-μm-core, 3-m-long, silica optical fiber (Thorlabs, Newton, NJ) using a 20-mm-focal-length quartz lens. The laser pulse energy was measured both preoperatively and postoperatively, using a pyroelectric detector (Gentec ED-200, Ste.-Foy, Quebec, Canada), and the laser pulse duration was measured using a photovoltaic infrared detector (PD-10.6, Boston Electronics, Brookline, Mass) connected to an oscilloscope (TDS 1002, Tektronix, Beaverton, Ore).

The Er:YAG and Ho:YAG laser parameters used in this study were chosen on the basis of reasonable clinical settings for tissue ablation. For example, the Er:YAG laser energy (20 mJ) was not equal to the Ho:YAG laser energy (500 mJ) because, on the basis of theoretical considerations, the Er:YAG laser energy is approximately 25 times more strongly absorbed by the tissue.
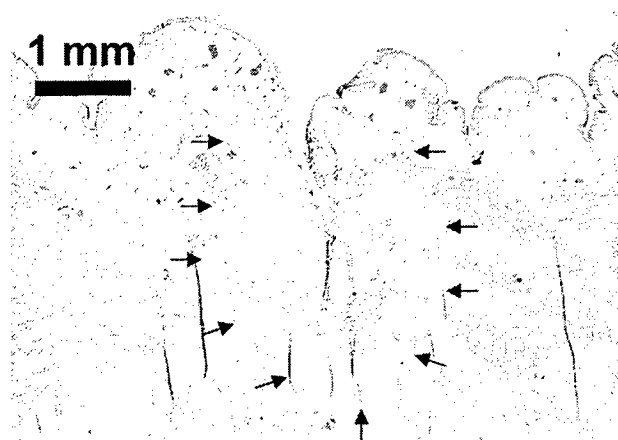
ANIMAL STUDIES

Our institutional Animal Review Committee (ACR No. SW01M293) approved all procedures. A total of 18 female domestic pigs (weight 30 to 45 kg) were divided into two arms, with 9 pigs in each arm, depending on the type of laser (Ho:YAG or Er:YAG) used. Three animals in each arm were killed on postoperative days (PODs) 0, 6, and 14.

After sedation with intramuscular acepromazine (0.39 mg/kg), atropine (0.07 to 0.09 mg/kg), and ketamine (15.0 mg/kg), general endotracheal anesthesia was induced intravenously by pentothal (5.0 to 7.0 mg/kg) and maintained with inhalation agents (1.5% to 2.0% isoflurane). Normal saline was given intravenously at a rate of 100 mL/hr until the end of the procedure. A preoperative dose of 1 g cephazolin was administered intravenously after intubation. Access to the urethra and bladder neck was obtained using a 17F rigid cystoscope (Karl Stortz, Tuttlingen, Germany) with a 30° lens. A laser fiber was passed through the working channel of the cystoscope, and, in each pig, three 1-cm-long incisions were made, two at the bladder neck (5-o'clock and
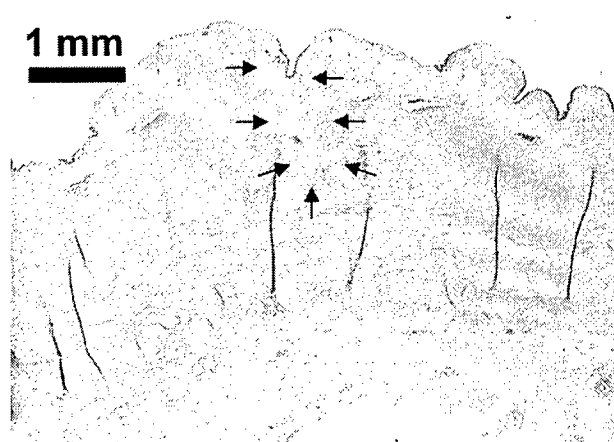
FIGURE 2. *Hematoxylin-eosin-stained histologic cross-sections of incisions made with (A) Er:YAG and (B) Ho:YAG laser on POD 6. Arrows demarcate border between native and thermally coagulated tissue.*

FIGURE 3. *Hematoxylin-eosin-stained histologic cross-sections of incisions made with (A) Er:YAG and (B) Ho:YAG laser on POD 14. Arrows demarcate border between native and thermally coagulated tissue.*
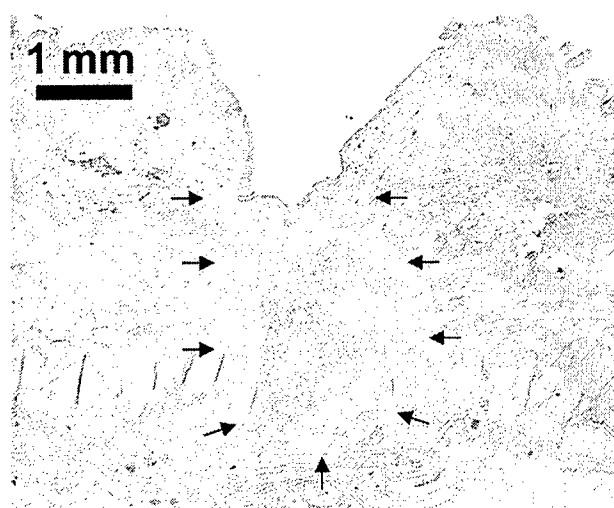
7-o'clock positions) and one in the mid-urethra (6-o'clock position). The incisions made with each laser were of equal depth (approximately 2.5 mm), and care was taken not to perforate the urethral and bladder wall. After completion of the procedure, a 14F urethral catheter was left in the bladder and removed 3 to 4 hours later. The animals were closely monitored postoperatively for signs of pain or distress and urinary problems.

The pigs were killed with an overdose of pentobarbital (150 mg/kg) in a method humane and consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association. The bladder and urethra were removed en bloc, bivalved, and grossly inspected to identify the incisions. The specimens were then fixed in formalin for further evaluation.

Histologic analysis was performed on all incisions by a trained pathologist (T.Y.C.). The pathologist was not blinded to the lasers used in this study. The tissue samples were processed using standard histopathologic techniques and stained with hematoxylin-eosin dyes. A transmission light microscope (Model E200, Nikon, Japan) was used to make quantitative measurements of the collateral injury and incision depth. The collateral damage on POD 0 was recorded as the coagulative necrosis measured from the incision outward and on PODs 6 and 14 as the extent of granulation width at the base of the

wound. The incision depths and amount of collateral damage were analyzed using Student's t test.

RESULTS

On POD 0, the incisions created in the mid-urethra and bladder neck using the Er:YAG and Ho:YAG lasers were of comparable depth, averaging 2540 ± 390 μm and 2530 ± 780 μm, respectively ($P = 0.49$). However, the zone of coagulative necrosis extending from each side of the incision (Fig. 1) was significantly greater in the Ho:YAG laser group than in the Er:YAG laser group (660 ± 110 μm versus 20 ± 5 μm, respectively; $P = 0.01$).

The postoperative collateral injury was identified as granulation tissue at the base of the wound. On POD 6 (Fig. 2), the width of the granulation tissue at the base of the incision created by the Er:YAG and the Ho:YAG lasers was 900 ± 100 μm and 2280 ± 700

TABLE I. *Injury parameters after incisions made with Ho:YAG and Er:YAG lasers at postoperative days 0, 6, and 14*

Laser Type	n	POD 0 Incision Depth (μm)	POD 0 Collateral Damage/ Coagulation Necrosis (μm)	n	POD 6 Incision Depth (μm)	POD 6 Collateral Damage/ Granulation Width (μm)	n	POD 14 Incision Depth (μm)	POD 14 Collateral Damage/ Granulation Width (μm)
Ho:YAG	3	2530 ± 780	660 ± 110	3	1500 ± 300	2280 ± 700	3	1240 ± 140	1580 ± 250
Er:YAG	3	2540 ± 390	20 ± 5	3	1100 ± 200	900 ± 100	3	670 ± 140	430 ± 100
P value		0.49	0.01		0.04	0.04		0.02	0.03

KEY: Ho = holmium; YAG = yttrium-aluminum-garnet; Er = erbium; POD = postoperative day.

μm, respectively ($P = 0.04$). Similarly, after 14 days, the amount of granulation tissue created by the Er:YAG laser remained significantly smaller than that formed by the Ho:YAG laser (430 ± 100 μm versus 1580 ± 250 μm, respectively; $P = 0.03$; Fig. 3).

As wound healing progressed, granulation tissue filled the wound bed and decreased the incision depth. At POD 6, the Er:YAG and Ho:YAG laser incisions were 45% and 60% of their initial depth (1100 ± 200 μm versus 1500 ± 300 μm, respectively; $P = 0.04$), implying that the injuries induced by the Er:YAG laser healed faster. On POD 14, the incisions from the Er:YAG and Ho:YAG lasers were 25% and 50% of their initial depth (670 ± 140 μm versus 1240 ± 140 μm, respectively; $P = 0.02$). This was consistent with the observation that the Er:YAG incisions were almost completely healed on direct endoscopic evaluation before death (Table I). Images of the tissue surface at 14 days also demonstrated accelerated wound healing after the Er:YAG incision compared with the Ho:YAG (Fig. 4).

COMMENT

The results of our study have confirmed the minimal collateral thermal damage caused acutely by the Er:YAG laser by gross and histologic examination. Histologic examination demonstrated that the Er:YAG laser produced approximately four times less scar tissue than the Ho:YAG laser. The granulation zone and incision depth were also less in the Er:YAG laser arm than in the Ho:YAG laser arm for a given POD. Incisions made with the Er:YAG laser healed more rapidly than those with the Ho:YAG laser. This difference was again evident even on gross examination of the specimens before formalin fixation. Incisions with the Er:YAG laser arm at POD 14 were difficult to identify because of the almost complete healing.

Although the Er:YAG laser is a promising new technology for potential clinical use in endourologic applications, the laser has several limitations. First, because of the precise cutting of the Er:YAG laser and the limited coagulation it produces, it is
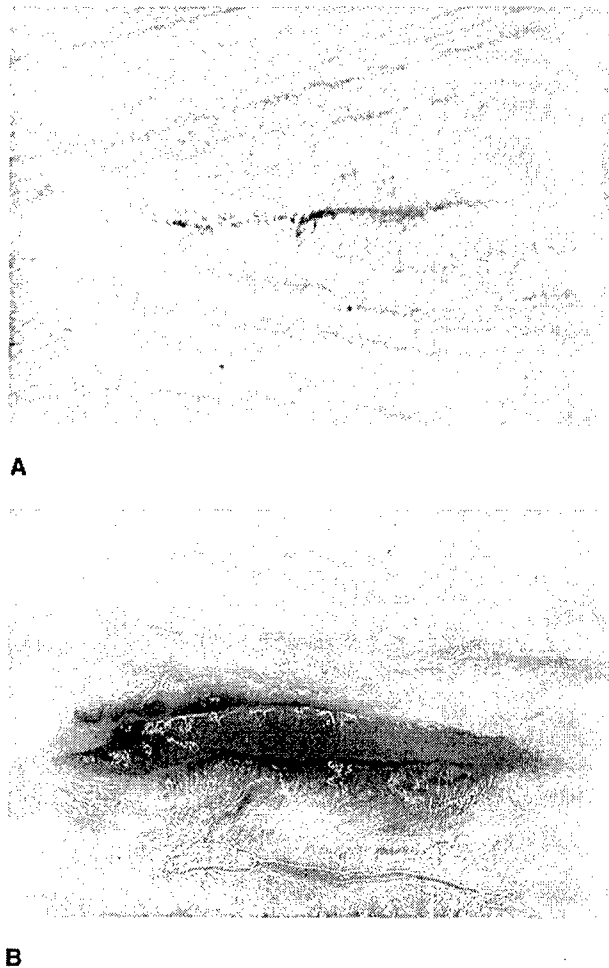

A

B

FIGURE 4. *Images of incisions made with (A) Er:YAG and (B) Ho:YAG lasers at POD 14.*

not recommended for applications requiring hemostasis. Bleeding was more pronounced during incisions with this laser, although this did not translate into any postoperative problems. Catheters were removed several hours after the procedure in all animals.

Second, conventional silica optical fibers do not transmit in the mid-infrared spectrum and therefore cannot be used at the 2.94-μm Er:YAG wavelength. Therefore, mid-infrared optical fibers are necessary for use with the Er:YAG laser. However,

commercially available optical fibers, including sapphire, germanium oxide, zirconium fluoride, and hollow silica waveguides have significant limitations. These fibers have either inferior mechanical and chemical durability or they are inflexible, toxic in tissue, and expensive. Although the sapphire fibers used in this study are adequate for use with rigid endoscopes in the lower urinary tract, these fibers are not sufficiently flexible for use with flexible scopes in the upper urinary tract.

Finally, the results presented in this short-term animal wound healing study referred to the incision of healthy, and not scarred, urethral and bladder neck tissue. It is predicted that the reduced water content in scar tissue compared with healthy tissue would result in greater thermal damage and scar formation after both Er:YAG and Ho:YAG incisions. However, because both lasers rely predominantly on water absorption for tissue ablation, the large differential in thermal damage and scar formation between the Er:YAG and Ho:YAG lasers reported in this study should remain.

CONCLUSIONS

Incisions created in the urethra and bladder neck of an animal model with the Er:YAG laser healed more rapidly and with less scar formation than incisions made with the Ho:YAG laser. Clinical studies are currently in development to evaluate use of the Er:YAG laser in the treatment of urethral strictures and bladder neck contractures.

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